Protocol for the BONE-RECON trial: a single-arm feasibility trial for critical sized lower limb BONE defect RECONstruction using the mPCL-TCP scaffold system with autologous vascularised corticoperiosteal tissue transfer

David S Sparks,1,2 Jay Wiper,3 Thomas Lloyd,3,4 Marie-Luise Wille,1,5,6 Marjoree Sehu,7 Flavia M Savi,1,5,6 Nicola Ward,8 Dietmar W Hutmacher,5,6,9 Michael Wagels5,10

ABSTRACT

Introduction Reconstruction of critical bone defects is challenging. In a substantial subgroup of patients, conventional reconstructive techniques are insufficient. Biodegradable scaffolds have emerged as a novel tissue engineering strategy for critical-sized bone defect reconstruction. A corticoperiosteal flap integrates the host's ability to regenerate bone and permits the creation of a vascular axis for scaffold neo-vascularisation (regenerative matching axial vascularisation—RMAV). This phase IIa study evaluates the application of the RMAV approach alongside a custom medical-grade polycaprolactone-tricalcium phosphate (mPCL-TCP) scaffold (Osteopore) to regenerate bone sufficient to heal critical size defects in lower limb defects.

Methods and analysis This open-label, single-arm feasibility trial will be jointly coordinated by the Complex Lower Limb Clinic (CLLC) at the Princess Alexandra Hospital in Woolloongabba (Queensland, Australia), the Australian Centre for Complex Integrated Surgical Solutions (Queensland, Australia) and the Faculty of Engineering, Queensland University of Technology in Kelvin Grove (Queensland, Australia). Aiming for limb salvage, the study population (n=10) includes any patient referred to the CLLC with a critical-sized bone defect not amenable to conventional reconstructive approaches, after discussion by the interdisciplinary team. All patients will receive treatment using the RMAV approach using a custom mPCL-TCP implant. The primary study endpoint will be safety and tolerability of this new technique.

STRENGTHS AND LIMITATIONS OF THIS STUDY
⇒ This study reports the trial protocol for a novel surgical approach to reconstruct bone and/or soft tissue in the setting of extensive critical size bone defects in the lower limb.
⇒ In line with the IDEAL framework, the trial is a phase IIa developmental clinical trial assessing safety and tolerability of this new technique.
⇒ The trial will also investigate time to bone union and weight-bearing status as secondary outcome measure.
⇒ The trial will serve as a platform for further prospective, randomised research into the use of this technique as its role expands for critical size bone defect reconstruction.

BACKGROUND

Reconstruction of critical bone defects in the appendicular skeleton may be challenging.1 The ambition to salvage a limb in critical-sized bone defects in the lower limb derives from an observed improvement in patient quality of life when compared with amputation and fiscal benefits to the community at large when patients resume premorbid activity.2 Most cases of critical-sized bone defects, with or without associated soft tissue defects, are amenable to reconstruction with conventional approaches. These include: limb shortening, non-vascularised autograft alone, delayed non-vascularised autograft placed into an induced membrane, distraction osteogenesis and vascularised bone with or without allograft.3,4 However, in a substantial
subgroup of patients, these conventional reconstructive techniques are not sufficient. Historically, these patients may end up with definitive treatment through limb amputation. This is the consequence of pragmatic limitations associated with non-flap-based options such as distraction osteogenesis and the limitations in harvestable autologous bone to reconstruct such large volumes. Tissue engineered scaffold biomaterials have emerged as a potential solution to this problem, when used in conjunction with contemporary reconstructive techniques.

Interdisciplinary research between our groups at the Centre for Regenerative Medicine (Queensland University of Technology, Brisbane, Australia) and the Australian Centre for Complex Integrated Surgical Solutions (ACCISS) has focused on the reconstruction of critical-sized bone defects for more than a decade. This has resulted in the bench to bedside translation of scaffold-guided bone regeneration (SGBR) using biodegradable composite scaffolds made from medical-grade polycaprolactone (mPCL) and tricalcium phosphate (TCP) using the human body as a bioreactor. In vitro, this scaffold system supports cell attachment, migration and proliferation with slow but sustained degradation to permit sufficient time for host tissue regeneration and remodelling with replacement of the scaffold by the patient’s own tissue. In vivo biocompatibility of this scaffold system has been studied in more than 100 small and more than 30 large animal studies. It may be augmented with growth factors such as recombinant human bone morphogenetic protein-7 (rhBMP-7), which are known to promote regeneration of bone. Importantly, the mPCL-TCP scaffold has been extensively evaluated in preclinical studies with a validated large animal critical-sized bone defect model developed by our group. Our research using this model has shown that this scaffold system used alongside rhBMP-7 and BMP-2 for a 3 cm and 6 cm critical-sized long bone defect leads not only to robust defect bridging but also biomechanically loadable large volume bone regeneration. This is a condition sine qua non for successful clinical translation.

Although osseoinductive scaffolds have been trialled in patients by a number of authors, there are a number of limitations that limit widespread clinical use. Scaffold vascularisation, which is inextricably linked to bone regeneration, remains key and its importance is generally underappreciated. A variety of methods have been investigated to address this issue including prevascularisation of scaffold prior to transplantation, vessel-based approaches for axial vascularisation (arteriovenous loop and associated variations) and flap-based approaches for axial vascularisation (muscle flaps, periosteal flaps etc). Clearly, a clinically efficacious method to vascularise a scaffold should also promote bone regeneration. The interface between the scaffold and the patient is also an important consideration as failure of the scaffold to be incorporated may result in resorption of adjacent native bone. Also, scaffolds that are not fully resorbable carry risks of implant failure or infection for the life of the implant, particularly if the implant is designed to be entirely load bearing.

The regenerative capacity of vascularised corticoperiosteal tissue is well recognised. It has a robust blood supply and potential donor sites for distant transfer are plentiful. For uniform scaffold vascularisation, an intrinsic approach is considered key. However, to date, a combined intrinsic and flap-based approach to scaffold vascularisation that also exploits the innate autologous regenerative capacity of corticoperiosteal tissue for bone regeneration has not yet been sufficiently explored. We define the coalescence of these concepts as regenerative matching axial vascularisation (RMAV), whereby a corticoperiosteal flap is used to vascularise scaffold intrinsically and also produce bone.

Between 2016 and 2018 we undertook a preclinical study evaluating the concept of RMAV by using a corticoperiosteal flap from the sheep hind limb and a three-dimensional (3D) printed mPCL-TCP scaffold to reconstruct both 6 cm and 3 cm intercalary defects of the tibia. This technique was compared against existing control data sets for this animal model. Control groups were reconstructed with autologous bone graft alone, mPCL-TCP scaffold alone. The RMAV approach showed enhanced bone volume regenerate on plain X-ray (XR) and micro-CT assessment and equivalent biomechanical torsional stiffness compared with bone graft alone (unpublished). In August 2017 we performed the first-in-human case of applied RMAV wherein a 3D printed mPCL-TCP scaffold with vascularised corticoperiosteal flaps and rhBMP-7 were used to successfully perform a reconstruction of the largest defect (36 cm) of load-bearing bone in the world to date. This work builds on our experience with bone defect reconstructive research. Eighteen months after the reconstructive procedure, the patient had produced a volume of regenerate bone that was sufficient to commence near complete weight-bearing on the limb and has subsequently achieved a high level of functioning in society. Assessment of further bone regeneration and defect healing is ongoing. We have since expanded on this with a case series involving a combination of load-bearing and non-load-bearing bone defect reconstruction using the RMAV technique.

Given our extensive preclinical research data set and evolving clinical experience, we feel that the logical next step in this emerging technique should be a robust feasibility clinical trial. Once the technique is established and appropriate outcome measures are clearly defined, it may then be appropriate to proceed to a randomised clinical trial in which RMAV is compared with other established clinical techniques for a given bone defect.

METHODS/DESIGN
Objectives
Hypothesis
The use of mPCL-TCP scaffold and autologous vascularised corticoperiosteal tissue transfer is a safe and feasible
approach to reconstruct critical-sized bone defects in the lower limb where conventional methods are not suitable.

Objectives

The primary objective of the BONE-RECON trial are to:
1. To determine the safety and tolerability of an mPCL-TCP scaffold with a vascularised corticoperiosteal tissue transfer for the reconstruction of weight-bearing long bone.

The secondary objective of the BONE-RECON trial are to:
2. To describe the clinically relevant outcomes after reconstruction with this novel technique.
   a. Time to clinical and radiological union.
   b. Functional outcome.
      i. Time to partial weight-bearing status.
      ii. Time to full weight-bearing status.
   c. Quality of life (36-item Short Form Quality of Life (SF-36) questionnaire responses).

Study design

The study is a registered, open-label, single-arm feasibility trial jointly coordinated by the Complex Lower Limb Clinic (CLLC) at the Princess Alexandra Hospital (PAH) in Woolloongabba (Queensland, Australia) of the Metro South Health Service (MSHS), the Australian Centre for Complex Integrated Surgical Solutions at the Translational Research Institute (Queensland, Australia) and the Centre for Regenerative Medicine at the Queensland University of Technology (Queensland, Australia). In line with the IDEAL framework, the trial is registered as a Phase 2a development trial for an innovative surgical intervention. With the aim of limb salvage, the study population includes any patient referred to the CLLC with a critical-sized bone defect not amenable to conventional reconstructive approaches after discussion by the multidisciplinary team (MDT) (ethics approval HREC/2020/QMS/52837).

Inclusion/exclusion criteria

Recruitment for this trial includes all adult patients up to 80 years of age presenting to the PAH CLLC with an acquired intercalary defect of the femur or tibia secondary to trauma (acute fracture and non-union) malignancy and infection. The defect must be of sufficient size that conventional means of reconstruction (Masquelet technique, distraction osteogenesis, vascularised bone transfer) would not be likely to succeed. Details for trial eligibility and the specific inclusion and exclusion criteria can be found in box 1.

Intervention

An mPCL-TCP 3D printed scaffold (Osteopore, Singapore) will be used in this project. The device has Federal Drug Administration (FDA) approval and has been used in a single selected case in Australia with Special Access Scheme class B approval, administered by the Therapeutic Goods Administration (TGA). This will be used alongside a free or pedicled tissue transfer of corticoperiosteal tissue to regenerate bone of sufficient volume and quality to bridge a critical-sized bone defect in the lower limb. The corticoperiosteal tissue from the medial femoral condyle and fibula are established donor sites in reconstructive surgery. The combination of the two methods for lower limb reconstruction, underpinned by the RMAV concept, is what makes this technique novel.

Patient selection/recruitment/enrolment

The CLLC is in receipt of Australia-wide referrals from a range of clinical specialties including infectious diseases, plastic and reconstructive surgery and orthopaedic surgical teams. The CLLC meets every 4 weeks at the Princess Alexandra Hospital. Referrals are accepted primarily from the MSHS catchment area but the CLLC will consider out of catchment referrals in circumstances where the clinic has unique expertise. Specific conditions assessed may include acute and subacute limb pathology (major acute fractures with segmental bone loss, bone malignancy, etc) or chronic limb pathology (osteomyelitis, infective non-union, etc). A flow diagram of the trial protocol is shown in figure 1.

On receipt of the referral and prior to clinical review, definitive imaging is organised. This includes plain XR, limb CT and/or MRI as well as white cell labelled whole body bone scan where appropriate. After clinical assessment, the imaging is reviewed with the attending radiologist and further imaging arranged as clinically indicated. As an MDT, the patient’s pathology is discussed and a
management plan proposed. Patients who are suitable for enrolment in the clinical trial would be identified and the extent to which they satisfy the inclusion and exclusion criteria is assessed by the co-coordinating principal investigator. Patients are then formally enrolled after written consent is obtained.

Patient and public involvement
Patients and/or public individuals were not involved in the design of this study and will not be involved in the conduct, reporting or dissemination of the research work.

Protocol
Prior to planning a reconstruction, the underlying pathology must be satisfactorily dealt with. The nature of the pathology and the time required to ensure that it has been adequately treated will determine the timing of the reconstruction with mPCL-TCP scaffold and vascularised corticoperiosteal tissue transfer. For acute/subacute pathology, this interval may be quite short and in some circumstances, may even be performed at the same time as the ablative surgery. In other conditions, such as osteomyelitis or infective non-union, it may take several months to ensure that the infection has been cleared. This would routinely include a 3-month period in which the patient takes no antibiotics to ensure there is no infective flare, suggesting a residual nidus of infection.

The implant design can then be commenced based on the most suitable imaging modality. In most cases, this will be a CT scan. The imaging data will be extracted from the PAH PACS (Picture archiving and communication system) and downloaded as a DICOM (Digital Imaging and Communications in Medicine) stack of files. These will be de-identified and transferred to the ACCISS workstation for segmentation by the ACCISS Clinically Applied Digital Innovations Engineer. The segmented object is then exported as an object file with an STL file extension to the computer-aided design (CAD) software (Materialise, Leuven, Belgium). Design tools in the CAD software will then be used to build the shell of a patient-matched implant that matches the patient’s anatomical landmarks and bridges the bone defect. Flanges and extensions to match the implant into the native bone for improved contact at the bone-implant interface will be incorporated into the design along with patient-matched features to incorporate the preferred method of fixation as directed by the treating orthopaedic surgeon. The designed implant is then validated by the coordinating principal investigator and orthopaedic surgeon.

Figure 1  Flow chart of study protocol. CPF, corticoperiosteal flap; MDT, multidisciplinary team; mPCL-TCP, medical-grade polycaprolactone β tricalcium phosphate; SF-36, 36-item Short Form Quality of Life questionnaire; SMFA, Short Musculoskeletal Functional Assessment; WC-labelled, white cell-labelled; XR, X-ray.
co-investigator, whereupon the de-identified bundle of files will be transferred using a secured web-based platform to the trial sponsor Osteopore. The team of engineers at Osteopore will then complete the design of the internal structure of the implant to ensure that it has suitable mechanical properties to tolerate implantation and physiological stresses. The final virtual design along with actual 3D printed prototypes will then be validated by the ACCISS Engineer, coordinating principal investigator, orthopaedic surgeon co-investigator and design team from Osteopore to ensure that the proposed implant is fit for purpose prior to manufacture.

Once the design is validated, the patient will be contacted and given a date for surgery. This includes standard preparation for surgery including assessment at the preadmission clinic by a specialist anaesthetist to ensure fitness for anaesthesia. Concurrently, the implant will be manufactured in triplicate in Osteopore’s clean room facility, sterilised, packaged with appropriate labelling and Instructions For Use and shipped to the PAH, where it will be stored in the sterilising department under suitable conditions, ready for use.

The reconstruction is performed at time 0. First, the bone void is stabilised with rigid fixation using the technique felt most appropriate by the treating orthopaedic surgeon. Chimeric vascularised corticoperiosteocutaneous flaps (CPCF) are then raised from whichever donor site or sites are felt most appropriate by the treating plastic surgeon. Typically, this would be from the ipsilateral fibula based on the peroneal vascular pedicle or the ipsilateral medial femoral condyle. The mPCL-TCP scaffold is manufactured and delivered in two parts, a posterior and an anterior component. The posterior component is inserted into the defect, working around the fixation device, with the endosteal extensions seated into the medullary space of the proximal and distal metaphyses. Once the posterior component is in place, the corticoperiosteal component of the mobilised and transferred CPCF is inserted and laid inside, such that the cortical bone raised with the periosteum is facing the neo-endosteal surface of the implant and the vascular pedicle sits deepest inside the scaffold. The lateral edge of the skin paddle is partially inset to the cutaneous defect and the target vessels prepared for microvascular anastomosis.

After the scaffolds and CPCF constructs were built around the fixation device, the vascular pedicle could be microsurgically anastomosed to the prepared target vessels under an operating microscope (Zeiss, Germany). Once flow is established, the anterior component of the 3D printed scaffold is inserted with the proximal and distal endosteal extensions positioned into the medullary canals of native adjacent bone. Tunnels to accommodate the perforators of the skin paddles for CPCFs are then carved into the anterior components of the 3D printed scaffolds using a 15-blade scalpel. The anterior and posterior components of the 3D printed scaffolds are secured to each other with two 3/0 Vicryl cerclage sutures (Ethicon, New Jersey, USA).

Generally, patients will remain in hospital for at least 2 weeks after surgical treatment. This reflects paramount conditions and may be a substantially longer period should surgical complications arise. A standard clinical protocol of graded limb compression, dependence and subsequently mobilisation follows. In uncomplicated cases, patients are reviewed at 1 month with plain XR and general clinical review followed by reviews at 3, 6, 12, 24 and 36 months. The final time point of patient assessment is 36 months. It is anticipated that most patients will achieve key endpoints prior to this milestone (generally by 24 months). Follow-up includes a routine clinical assessment, plain radiograph of the reconstructed limb ± a CT scan. The focus of these assessments is to identify complications and establish clinical and radiological evidence of union, after which time full weight bearing may commence as directed by the treating orthopaedic and plastic surgeons. Functional and quality of life assessments, the SF-36 questionnaires, respectively, will be performed by dedicated physiotherapy/occupational therapy staff involved in the trial. More frequent follow-up may be arranged according to clinical need.

Data collection
Data collection and reporting will be performed in concert with the Consolidated Standards of Reporting Trials guidelines.23 A Trial Steering Committee (TSC) will be established to supervise the trial and will liaise with the Data Monitoring Committee (DMC) directly (HREC/2020/QMS/52837). This will include an independent chair and two non-independent chairs. Several other participants will be included in the TSC from the Metro South HREC (independent) and the MDT (non-independent).

Endpoints
The key primary endpoints for this single-arm study are safety and tolerability. The primary outcome measures will be evaluated at 3 months to determine if the reconstructive approach is feasible at this early time point and if it is safe and well tolerated by the patients. This prospective trial data will aim to confirm already existing case series data we have reported to date, which suggests that this approach is safe and well tolerated.21 In terms of safety and tolerability, the methods used in this prospective trial are a variation to conventional standard of care which for these patients may be amputation. Specific reporting on safety and tolerability will include adverse events that occur during the study period as related to both the scaffold and surgical approach. Reporting will be performed as an ‘adverse event’ and ‘near adverse event’, as per the Australian TGA guidelines on Medical Device Adverse Event Reporting.24 Monitoring of the safety of the intervention will be conducted by the DMC.

The secondary outcome measures are the time to union (radiological and/or clinical), and functional outcome measures on the treated limb including weight-bearing (partial and full) and SMFA questionnaire response. In
a descriptive method, these secondary endpoints will inform whether clinically useful bone union occurs in these patients and its relationship to functional outcomes.

Union will be assessed by a dedicated radiology consultant involved in the trial and scored using the radiological union score and the CT union score. Clinically, union will be assessed by both the consultant orthopaedic surgeon and plastic surgeon using a combination of clinical examination alongside assessment of weight-bearing status and gait where applicable. The latter is performed in conjunction with a dedicated physiotherapist involved in the trial. For the purposes of the trial, partial weight-bearing will involve a small amount of weight to be loaded on the affected extremity during ambulation, with the weight gradually increased so that the patient can ambulate but still needs the use of an ambulatory device like a cane or crutches. The latter also includes touch weight bearing on the affected limb. Full weight bearing will include patients where there is no clinical limit to weight bearing on the affected.

Functional outcome is more difficult to measure reliably. In this trial it will be assessed with the SMFA questionnaire. For quality of life, the SF-36 questionnaire by a dedicated occupational therapist and physiotherapist involved in the trial. These questionnaires are provided to the patient for self-reporting at each review time point. Both the SMFA and the SF-36 are well validated for the assessment of lower limb reconstruction.

Withdrawal Subjects may withdraw from the study at any time or may be discontinued at the discretion of the treating surgeon. They may also be withdrawn if the investigator makes a decision to terminate the study. Treatment after the study will be at the discretion of the treating surgeon.

Statistical analysis No formal power analysis has been performed as this is not a comparative study. The number of patients required for inclusion in the trial is based on in vivo data in an ovine large animal model and is sufficient to meet the primary end points of early feasibility, safety and tolerability. All patients registered for the trial will be accounted for in the analysis (intention-to-treat). For secondary outcome measures, statistical analysis otherwise will include a descriptive review of relevant clinical variables to the time to bony union and time to weight-bearing on the affected limb in the study period. Univariate student’s t-test, χ² and multivariate Cox regression analysis will be performed where it is statistically appropriate. For such measures, statistical significance will be defined as p<0.05. Data will be analysed and graphed using SPSS for Windows V.26 (SPSS, Chicago, Illinois, USA).

DISCUSSION
This study aims to evaluate the role of an original scaffold-guided bone regeneration (SGBR) protocol incorporating autologous vascularised corticoperiosteal tissue transfer for the reconstruction of complex lower limb defects with large volume bony loss. The current trial builds on successful preclinical work performed by our group evaluating this technique in a well-characterised and validated large animal model and it is supported by a successful clinical experience in a recently published case series.

From basic principles, the simplest pathway to generating tissue through SGBR should be to combine a bioresorbable scaffold with a vascularised autologous flap, the constituents of which are of the specific tissue type intended for regeneration along with its progenitor cells. A clear example of this would be to use a corticoperiosteal flap to vascularise a scaffold intended for bone regeneration, as we have done in our preclinical work. This approach may obviate the need for cell culture-based approaches (such as mesenchymal stem cell culture and scaffold implantation) that aim to enhance bone regeneration. In essence, the osteogenic potential of the corticoperiosteal flap provides sufficient host-derived osteogenic growth factors, periosteal-derived mesenchymal stem cells and the appropriate extracellular environment essential for new bone growth—as seen with fracture healing. This applies the Gilles-Millard principle of a like for like reconstruction to surgical prefabrication and is termed regenerative matching axial vascularisation.

Using this approach, it would seem that the highest yield through the in vivo bioreactor principle can be achieved while incorporating a reliable pattern of intrinsic axial vascularisation to the scaffold to sustain the necessary vascularity required for ongoing bone regeneration.

The mPCL-TCP scaffold to be used in the trial has been studied extensively in a preclinical setting and already has a clinical efficacy record, with approval for use in the craniofacial region by the FDA (USA), TGA, CE (Conformite Europeenne) marking and more than 20000 clinical cases confirming efficacy and safety.

The scaffold is biocompatible with a controllable degradation rate through hydrolysis that appears to occur over 24–48 months, thereby permitting a gradual replacement of the scaffold by bone without compromising the structural integrity of the construct. Data from this trial are likely to further validate the role of the mPCL-TCP scaffold system in the setting of converging SGBR and microvascular surgery and extend its role to a range of load-bearing reconstructive applications.

This project has a number of benefits, both to individuals and to society at large. First, for an individual, patients can be offered an alternative to amputation where bone loss exceeds the capability of conventional reconstructive techniques. Given the established long-term functional benefits offered through limb salvage and reconstruction, it is expected there will be flow-on effects for the patient from a psychological point of view as well. From a society point of view, in the setting of major trauma, cost-associated benefits from limb salvage are significant in the long-term (≥7 years) when
contrasted to primary limb amputation ($A232,562 vs $A725,360). Therefore, a limb salvage approach that optimises outcomes in challenging cases of limb injury with extensive bone loss is required. Also, it may be that RMAV-based reconstructions can be shown in the future to outperform conventional reconstructive techniques for smaller volume defects, both in terms of time to healing and cost-benefit.

Tissue Engineering & Regenerative Medicine research, particularly in bone regeneration, has considerably expanded over the last 20 years. Interestingly, few concepts have translated into routine clinical use. This may be related to the historical disconnect of the tissue engineering community in large to plan and manage successfully the translation from bench to the bedside. To overcome this, it is important that scientific experimentation and clinical application are rooted in evidence-based preclinical data sets using validated models and a translatable approach. This clinical trial not only builds on the most comprehensive preclinical data sets found in the tissue engineering literature today but includes many of the pioneers of the SGBR methodology moving forward into clinical application.

**Trial status**

Formal trial recruitment is expected to begin in late 2023 and conclude in 2027-2028, with an interim analysis occurring after five patients (50%) have completed 36 months follow-up post-treatment. Full analysis will be undertaken at the conclusion of the study.

**Author affiliations**

1 Queensland University of Technology, Faculty of Engineering, Brisbane, Queensland, Australia
2 The University of Queensland PA Southside Clinical School, Woolloongabba, Queensland, Australia
3 Department of Plastic & Reconstructive Surgery, Princess Alexander Hospital, Woolloongabba, Queensland, Australia
4 Department of Radiology, Princess Alexander Hospital, Woolloongabba, Queensland, Australia
5 ARC Training Centre for Multiscale 3D Imaging, Modelling and Manufacturing, Queensland University of Technology, Brisbane, Queensland, Australia
6 School of Mechanical, Medical, and Process Engineering | Faculty of Engineering, Queensland University of Technology, Brisbane, Queensland, Australia
7 Department of Infectious Diseases, Princess Alexandra Hospital, Woolloongabba, Queensland, Australia
8 Department of Orthopaedics, Princess Alexander Hospital, Woolloongabba, Queensland, Australia
9 Faculty of Health, School of Biomedical Sciences, Queensland University of Technology, Brisbane, Queensland, Australia
10 Australian Centre for Complex Integrated Surgical Solutions (ACCISS), Translational Research Institute Australia Qhrelin Research Group, South Brisbane, Queensland, Australia

**Acknowledgements** We acknowledge indirect financial support by grants awarded through the Australian Research Council; National Health and Medical Research Council, Princess Alexander Hospital Research Foundation; and Wesley Research Foundation, Brisbane. The current trial is an investigator-initiated trial funded by Osteopore (Singapore). The funders play no role in the study design, surgical treatment, collection, management, analysis and interpretation of data or the final report and its publication, nor do they have ultimate authority over any of these actions. Availability of data and materials and access to all data sets and statistical code will be granted individually upon request.

**Contributors** Study conception and design: DSS, JW, TL, M-LW, MS, MW, and DWH. Acquisition of data: DSS, FMS, and MW. Data monitoring and statistical analysis: DSS and MW. Analysis and interpretation of data: DSS and MW. Drafting of manuscript: DSS, JW, TL, M-LW, MS, FMS, NW, DWH and MW. Critical revision: DSS, MW and DWH. All authors read and approved the final version of this manuscript. Authorship eligibility guidelines according to the ICMJE were followed. The use of professional writers is not intended.

**Funding** The primary sponsor for the trial is Osteopore (Osteopore International, Singapore).

**Competing interests** DH is a shareholder in Osteopore (Osteopore International, Singapore). The remaining authors declare no competing interests relating to this paper.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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**ORCID iD**

David S Sparks http://orcid.org/0000-0002-6495-3770

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