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PROTOCOL TITLE:

Matrix-Directed Therapy In Older Adolescents And Adults With Osteogenesis Imperfecta – The "MOI-A" Study

SHORT TITLE:

MOI-A

NOTE: The SPIRIT 2013 Statement provides evidence-based recommendations for the minimum content of a clinical trial protocol. *"SPIRIT is intended to facilitate the drafting of protocols and improve their completeness. High-quality protocols can promote proper trial implementation, reduce avoidable protocol amendments, and facilitate full appraisal of the study's scientific and ethical considerations".*

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FULL TITLE OF THE TRIAL:

Matrix-Directed Therapy In Older Adolescents And Adults With Osteogenesis Imperfecta – The "MOI-A" Study

SHORT TITLE:
MOI-A

PROTOCOL VERSION NUMBER AND DATE:

Version 1.1 08.08.2023

FUNDER:

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SPONSOR:

Sheffield Children's NHS Foundation Trust

CHIEF INVESTIGATOR:

Professor Nicholas Bishop

RESEARCH REFERENCE NUMBERS:

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REC REFEREENCE NUMBER: 23/LO/0158
EudraCT NUMBER: *[to be added]*
ISRCTN NUMBER: [ISRCTN13317811]

NOTE: This study is an international collaboration with Italy. However, each country has its own approved version of the protocol and sponsorship arrangements following country specific regulations. This is the UK version of the protocol which has been approved by the MHRA. The Italian protocol matches the UK version in relation to Master components of the study: intervention, pharmacovigilance and data collection. The Italian protocol will be approved by the local and national competent authorities before recruitment can commence in Italy.

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SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) Standard Operating Procedures (SOPs), and other regulatory requirements as amended.
I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

For and on behalf of the UK Sponsor:

Signature: DocuSigned by: Keith Pugh 9347C780FAA2428... Date: 04-Sep-2023 | 14:08 BST

Name: Keith Pugh

Position: R&D Manager

Chief Investigator Signature: DocuSigned by: Nicholas Bishop 622EFA816F9A47C... Date: 04-Sep-2023 | 06:03 PDT

Name: Professor Nicholas Bishop

Statistician Signature: DocuSigned by: Chao Huang 0D5472B0731C4DA... Date: 04-Sep-2023 | 14:16 BST

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FUNDER	UKRI funded as part of a wider programme REMEDi4ALL within the Horizon Europe Topic HORIZON-HLTH-2021-DISEASE-04-02 Proposal number: 101057442 Proposal acronym: REMEDI4ALL
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Protocol amendments since Version 1.0

Version	Date	Summary of Changes

KEY WORDS

Osteogenesis imperfecta, losartan potassium, bone turnover, LSC, CTX, TGFβ

ROLES AND RESPONSIBILITIES OF STUDY GROUPS AND INDIVIDUALS

• **The UK Sponsor** (Sheffield Children's Hospital NHS Foundation Trust) will have overall responsibility for the conduct of the study in the UK. The study will be managed by the HHTU, on behalf of Professor Bishop (Chief Investigator). The study will be monitored by HHTU in accordance with Standard Operating Procedures (SOP) to ensure compliance with UK Clinical Trial Regulations. All study related documents will be made available upon request for monitoring and for inspection by the Medicines and Healthcare products Regulatory Agency (MHRA) (if requested).

• **Chief Investigator(s)** - The Chief Investigator will have responsibility for the design, coordination and management of the study.

- Trial authorisation including responsibility for the protocol and obtaining approvals from the MHRA, Research Ethics Committee (REC) and Research & Development (R&D)
- Ensuring that the study is conducted according to the UK Clinical Trial regulations and Good Clinical Practice (GCP)
- Assessment of SAEs and expedited reporting of any SUSARs

• **Hull Health Trials Unit (HHTU):** duties will be defined in the collaboration agreement.

• **Statistical Analysis** – [Chao Huang] will oversee statistical aspects of the study including drafting the analysis plan, conduct of analyses and reporting of results.

• **The Principal Investigator** at the participating site will be responsible for site conduct of the study. The Investigator Site File will be maintained by the study team, overseen by the Principal Investigator.

• **UK Site Teams** will consist of GMC registered clinicians responsible for approaching patients, confirming eligibility, obtaining consent and undertaking clinical assessment of Serious Adverse Events/Reactions. The PI support team will facilitate the consent process, coordinate implementation of study interventions and data collection, process safety reports and prepare for monitoring visits. Sites will conduct the study in accordance with the protocol, SOPs, study agreements, the UK Clinical Trial Regulations and GCP.

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GLOSSARY OF ABBREVIATIONS

aBMD	areal bone mineral density
AE	Adverse Event
ALD	After Last Dose
APR	Annual Progress Report
BMI	Body mass index
BP	Blood pressure
BSALP	bone-specific alkaline phosphatase
CI	Chief Investigator
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CTU	Clinical Trials Unit
CTX	Carboxy-terminal crosslink of type I collagen telopeptide
DMEC	Data Monitoring and Ethics Committee
DXA	Dual Energy X-ray Absorptiometry
eTMF	electronic Trial Master File
FBC	Full Blood Count
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
HHTU	Hull Health Trials Unit
HRA	Health Research Authority
HRpQCT	High Resolution peripheral Quantitative CT
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ID	Identification
IFCC	International Federation of Clinical Chemistry and Laboratory Medicine
IMP	Investigational Medicinal Product
IOF	International Osteoporosis Foundation
ITT	Intention-to-treat
LFTs	Liver Function Tests
LSC	Least significant change
MCP-Mod	Multiple Comparison Procedure – Modelling
mg	Milligram
MHRA	Medicines and Healthcare products Regulatory Agency
NCI-CTCAE	National Cancer Institute of Common Terminology for Adverse Events
OBD	Optimal Biologic Dose
OD	Once Daily
OIM	OI mice
OI-QoL	Osteogenesis Imperfecta quality of life
P	Pulse
P1NP	Procollagen type 1 N-propeptide
PI	Principal Investigator
PIS	Participant Information Sheet
pISF	paper Investigator Site Files
RCC	REDCap Cloud
R&D	Research & Development
REC	Research Ethics Committee
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SAS	Safety Analysis Set
SCH	Sheffield Children Hospital
SIV	Site Initiation Visit
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SSG	Study Steering Group
STH NGH	Sheffield Teaching Hospitals Northern General
SUSAR	Suspected Unexpected Serious Adverse Reaction
TGFβ	Transforming growth factor beta
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
TSP1	thrombospondin-1
U&Es	Urea and Electrolyte
ULN	Upper Level of Normal
uNTX	urinary amino-terminal crosslink of type I collagen telopeptide
WOCBP	Women of child bearing potential

CONTENTS

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TRIAL SUMMARY

NOTE: This study is an international collaboration with Italy. However, each country will have its own approved version of the protocol. This is the UK version.

Study title	Matrix-Directed Therapy In Older Adolescents And Adults With Osteogenesis Imperfecta – The "MOI-A" study	
Short title	MOI-A	
Clinical phase	Randomised control trial phase II/pilot	
Trial design	Open label dose escalating (final dose assigned randomly)	
Trial participants	Older Adolescents and Adults aged 16 years and above with Osteogenesis Imperfecta Approximately 150 eligible patients known in UK [n=75] and Italy [n=75]	
Sample size	Total study sample size is 30 Aiming for 15 to be recruited in each country but recruitment will be competitive	
Investigation	Thirty participants will be randomised at baseline to one of three "final doses" - 25, 50 or 75mg once daily. All participants will start on 25mg once daily. Those assigned to higher "final doses'' will increase in 25mg once daily increments on Day 8 and Day 15 following safety assessments to develop a final estimate of Optimal Biologic Dose (OBD).	
Planned trial period	A 24 week study medication treatment period excluding the screening period	
Follow up	None	
	Objectives	**Outcome Measures**
Primary	• To establish the effective dose of losartan in 30 older adolescents and adults aged 16 years and above with OI, based on maximal reduction in the bone resorption marker carboxy-terminal crosslink of type I collagen telopeptide (CTX)	• Percentage change in CTX over the 24 week period of the study
Secondary	• To determine the changes in proxy efficacy outcomes for bone (turn over, mass, architecture and strength) using blood test, High Resolution peripheral Quantitative CT (HRpQCT), Dual Energy X-ray Absorptiometry (DXA) and muscle (strength) using the "Timed Up and Go" test • To determine changes in quality of life using a validated disease-specific tool (OI-QoL)	• Percentage change in CTX at week 8 • Percentage change in TGFβ & P1NP at week 8 • Percentage change in TGFβ & P1NP over the 24 week period of the study • Change in DXA LSaBMD • Change in radial and tibial total vBMD by HRpQCT • Change in Timed Up and Go test • Change in OI QoL
Investigational Medicinal Product	Losartan Potassium	

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Formulation, Dose, Route of Administration	Oral administration administered as 25mg film-coated tablets in doses of 25, 50 or 75mg once daily
Eligibility criteria	**Inclusion criteria:** • Age 16 years and above • Diagnosed with osteogenesis imperfecta (any type) • Prior treatment with up to and including 6 weeks of oral bisphosphonate therapy is allowed provided there has been a 12 month washout period since the last dose of treatment. • Prior treatment with a single dose of an intravenous bisphosphonate is allowed provided there has been an 18 month washout period since the treatment was given. • Prior treatment with a single dose of denosumab is allowed provided there has been a 12 month washout period since the treatment was given. • A WOCBP who agrees to use an effective contraceptive method from point of signing the informed consent. • Agreed not to participate in another interventional research project during their involvement in this study. • Not taking prohibited concomitant medications, listed in exclusion criteria. • Any other contraindication that makes the patient unsuitable to take part in the study in the opinion of the investigator.
	Exclusion criteria: • Current use of losartan • Prior use of losartan within preceding 6 month to enrolment • Presence of other chronic illnesses including renal failure likely to affect bone metabolism or structure. • Known severe hypotension resulting in dizziness, fainting or headaches. • Hyperkalaemia. • Current medication that increases potassium retention, or may increase potassium levels. • Current medication with lithium. • Current medication with other substances which may induce hypotension. • Currently taking oral bisphosphonates or intravenous bisphosphonates. • Prior treatment with more than 6 weeks oral bisphosphonates treatment. • Prior treatment with more than a single dose of intravenous bisphosphonate. • Prior treatment with more than one dose of denosumab. • Recent (last 12 months) or current treatment likely to affect bone – this does not include inhaled or intermittent oral therapy with steroids for asthma (no more than three months of oral steroids in previous 12 months).

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	• Severe Hepatic impairment • Renal impairment (GFR<60ml/min/m2) if treated with aliskiren-containing products • Diabetes mellitus if treated with aliskiren-containing products • Cardiac failure treated with diuretics • Pregnancy or lactation • Known hypersensitivity to losartan or any of the excipients • Recent fracture in the prior 6 months to enrolment
Investigations performed	Pubertal stage assessment; Fracture incidence; Physical and clinical exam; BMI [Height, Weight]; Vital signs: BP, P, Temperature, Respiratory rate, O_2 Saturations; Urine pregnancy test (WOCBP); HRpQCT Scan radius and tibia; DXA LS and Hip; Timed "up and go" test; QoL questionnaire
Biological samples	Blood tests [FBC, U&Es, LFTs]; Fasting blood tests [CTX, losartan TGFβ, P1NP, Bone profile 25OHD, PTH]; Urine dipstick
Planned trial sites	3 UK Sites and 3 Italian sites

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1.0 INTRODUCTION

Osteogenesis imperfecta

OI is the commonest inherited cause of bone fragility (approx 1 in 16,000). People with OI suffer bone fragility causing fractures, pain and deformity; sarcopenia causing fatigue and poor endurance; aortic root dilatation and hearing loss. The range of severity is broad with severely affected individuals at risk of early death e.g. from respiratory failure in infancy, or progressively deforming bone disease that leaves them permanently wheelchair bound with scoliosis, basilar invagination and intractable pain. Even the more mildly affected individuals have an increased risk of fracture and suffer with easy fatigability.

Current standard of care and potential benefits to health

No drug currently has market authorisation to treat OI. Current standard-of-care is multidisciplinary, with pharmacological interventions – primarily bisphosphonates[1] - directed at increasing bone mass; however, such interventions are of equivocal efficacy.[2] The structural damage that can accumulate as a result of repeated fractures over time may not be reversible. The lack of a treatment with clearly defined efficacy in terms of reducing fracture frequency or the sarcopenia that is increasingly recognised in this condition leads to the consideration of alternatives based on what is known about the molecular pathophysiology of the condition.

Existing approaches to the treatment of OI focus on increasing bone mass as a means to address the loss of bone mass, degradation of microarchitecture and the alteration in bone material properties that renders the bone brittle. We suggest that by reducing circulating Transforming growth factor beta (TGFβ) levels (see below for supporting evidence) through the use of our intervention, we will both reduce bone turnover and bone loss, reducing fracture risk and need for orthopaedic interventions, and have a positive effect on muscle function and quality of life. This is a novel approach that has not been studied previously in a clinical setting.

Service, current policies and priorities

Services for adults with OI are less well developed in terms of the multidisciplinary approach than for children. In the UK, NHS England are consulting on a plan to develop a rare bone disease network, but funding is not yet in place to support this. The main priorities identified by adults with OI for future research include measures to improve quality of life, and reducing fracture frequency.

1.1 PRE-CLINICAL DATA

Recent studies in murine OI models showed increased TGFβ-pathway signalling activity – cause unknown - and increased expression of TGFβ target genes.[3] Use of a murine pan-TGFβ neutralising antibody 1D11 in a severe OI mouse model (Crtap-/-) reduced bone resorption (CTX biomarker 25%±5% lower) and significantly increased spine bone volume (235% increase in BV/TV).[3]

Activation of the AT1 receptor results in downstream signalling through p38 MAPK, JNK and ERK1/2, with up-regulation of thrombospondin-1 (TSP1) production and subsequent increase in TGFβ. TSP1 is present in bone tissue and substantially increased in OI bone.[4] Losartan and its active metabolite E3174 are AT1 antagonists. We hypothesised that AT1 receptor blockade using losartan would reduce circulating TGFβ and consequently bone loss. Our preclinical data from dosing OI mice (*OIM*) with placebo vs losartan 0.6g/l in drinking water for 4 weeks shows

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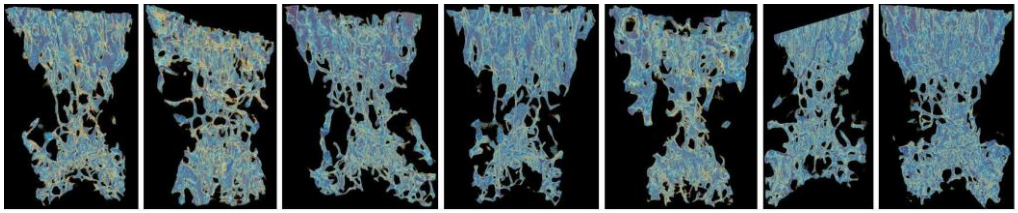
reduced bone resorption: CTX: 276(100) vs 157(50)ng/ml – 43% reduction; p=0.0204 and TGFβ: 79.2(14.6) vs 60.0(18.6) ng/ml – 24% reduction; p=0.0440, respectively. 8 weeks of treatment at 0.6g/l resulted in a 6 fold difference in vertebral bone mass by microCT; BV/TV 63.8(40.0)% vs 10.0(2.0)%, p=0.0215.

The following images (Figure 1) illustrate the changes in bone density in murine models

Control



Treated

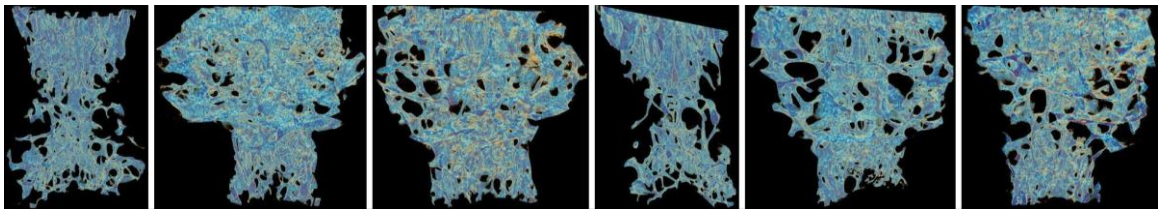


FIGURE 1: REPRESENTATIVE IMAGES OF OI CHANGES IN MURINE MODEL

Main Research Question

We hypothesise that losartan will reduce bone turnover in older adolescents and adults with OI by reducing circulating levels of TGFβ and hence TGFβ pathway signalling, which has been demonstrated in mouse models of OI to improve bone mass and architecture. We aim to identify the dose of losartan that is effective in reducing circulating levels of CTX, a bone resorption (destruction) marker, without causing undue side effects.

Based on murine model studies, this study hypothesises that the pathway of AT1-initiated TGFβ signalling has a positive influence on bone density in adolescents and young adults with OI, see figure 2 the following image:

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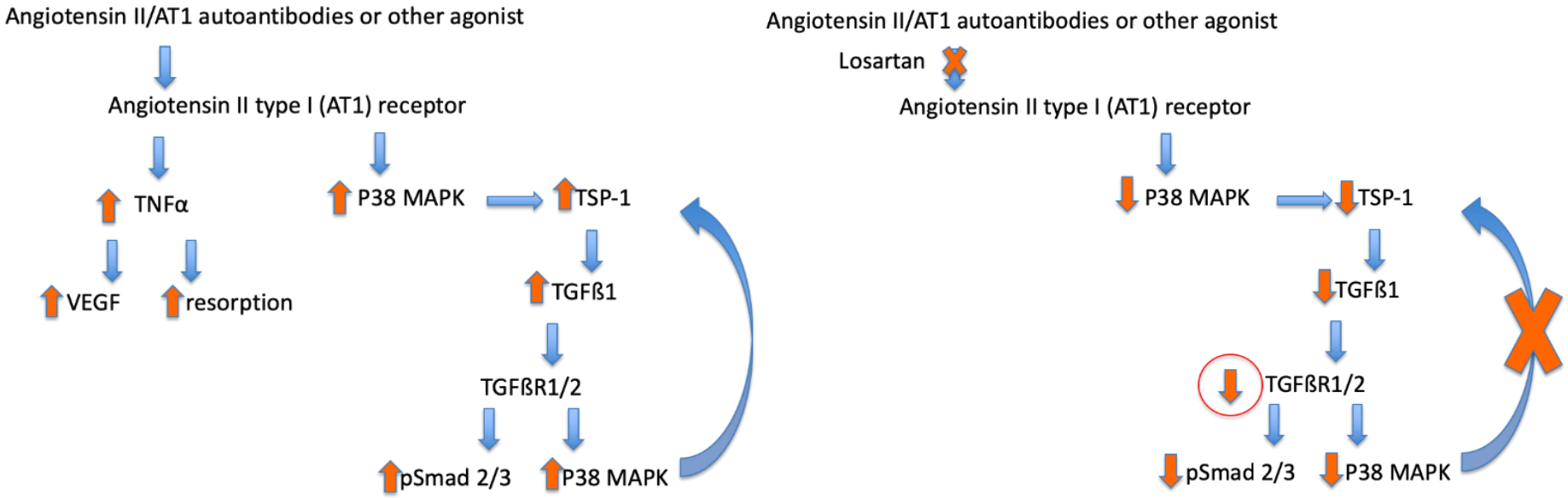

FIGURE 2: AT1-INITIATED TGFB SIGNALLING AND THE EFFECT OF LOSARTAN

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1.2 EVIDENCE GAPS AND STUDY RATIONALE

1.2.1 PRIMARY CLINICAL OBJECTIVE

Our primary clinical objective is to establish the effective dose of losartan in 30 older adolescents and adults aged 16 years and above with OI, based on maximal reduction in the bone resorption marker carboxy-terminal crosslink of type I collagen telopeptide (CTX).
Reducing bone turnover may reduce fracture risk in this population.
Measuring or predicting the efficacy of an anti-fracture intervention over short time periods is the participant of continuing debate. Monitoring fracture frequency over short time periods is unlikely to be an effective method, unless the incident fracture rate is very high. In addition, anti-fracture medications reduce fracture risk rather than eliminating it, so an incident fracture may not reflect lack of efficacy.

Proxy markers for the efficacy of interventions designed to increase bone strength and thus reduce fracture risk are used in both industry and investigator led studies, with the support of regulatory authorities.

Determination of the change in areal bone mineral density (aBMD) at either the lumbar spine, hip, or both, over one to two years has become the preferred method of assessing intervention efficacy, supported by some international organisations as well as regulators. However, this approach may result in some patients receiving an ineffective treatment over a prolonged time period; some patients may also not have a change in aBMD that is greater than the Least Significant Change (LSC) for the measurement.[5]

Whilst there is no clear evidence that the change in any short term marker has an unambiguous relationship with fracture risk reduction, it has been suggested for some time that changes in bone turnover markers including the bone formation markers serum bone-specific alkaline phosphatase (BSALP), serum procollagen type 1 N-propeptide (P1NP) and the bone resorption markers serum carboxy-terminal crosslink of type I collagen telopeptide (CTX) and urinary amino-terminal crosslink of type I collagen telopeptide (uNTX) could be used to assess the response to interventions designed to reduce fracture risk, and might be predictive of efficacy. BSALP and P1NP reflect the activity of bone-forming cells; CTX and uNTX measure the cross-linked peptides produced during the process of the breakdown of collagen in bone tissue.

1.2.2 WHAT IS THE EVIDENCE TO SUPPORT THE USE OF CTX AS THE BIOMARKER THAT INDICATES WHETHER LOSARTAN HAS HAD AN EFFECT?

Both bone resorption and bone formation are increased in OI.[6] The net effect of this activity is reduced bone mass, degraded microarchitecture and, in combination with the altered material properties of the bone tissue itself, increased bone fragility. Interventions that reduced bone resorption such as bisphosphonates have been shown, particularly in children with mild OI, to reduce fracture frequency.[1,7] Data supports using change in bone resorption marker(s) to assess the response to interventions in this situation. Our preclinical data from the OIM mouse model shows that losartan 0.6g/l (as opposed to placebo) for 4 weeks reduced bone resorption: CTX: 276(100) vs 157(50)ng/ml; p=0.0204. The same dose of treatment for 8 weeks increased vertebral bone mass six-fold - BV/TV%; 63.7 (40.0) vs 10.0 (2.0) p=0.0215

1.2.3 IS CTX PRECISE ENOUGH TO BE USED FOR THIS PURPOSE IN THIS CONTEXT OF USE?

A position paper on behalf of the International Osteoporosis Foundation (IOF) and the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) reviewing the literature in 2011 cited a number of national and international groups' consensus documents that identified serum CTX as the bone resorption marker of choice. The authors suggested the use of Least Significant Change (2.77 x biomarker %CV) as a guide

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to a target threshold for reduction in CTX that would indicate efficacy.[8] Serum CTX, when taken appropriately – fasting at between 7.30-09.00 AM - is preferred to urine NTX because it has significantly lower intra-participant variability.[9]

The LSC for serum CTX was estimated for a population of women aged 55-77 based on repeated measures at baseline before initiating lasofoxifene (a selective oestrogen receptor modulator, SERM) treatment; the value for %CV was 9.97% and thus for LSC was 27.7%.[10] Approximately half the treated individuals achieved a reduction equal to or greater than the LSC by 4 weeks, significantly different to the placebo group with that difference maintained to study end. In that study, changes in bone resorption (uNTX) correlated negatively with the change in lumbar spine aBMD, i.e. aBMD rose as uNTX fell. There were no differences in numbers of reported fractures (1 hip fracture in each group), reflecting the small study size.

1.2.4 IS CTX SUFFICIENTLY RELATED TO A CLINICALLY IMPORTANT OUTCOME TO USE FOR THIS PURPOSE?

A meta-analysis of the relationship between short term reduction in bone turnover markers and subsequent fracture risk in placebo-controlled trials of anti-resorptive agents, primarily oral and intravenous bisphosphonates and SERMs, was published in 2018. The analysis included 14 large scale studies performed over the period from 1995-2010. There was a relationship between progressive reduction in CTX and progressive reduction in vertebral fracture frequency; the relationship was less strong for non-vertebral and hip fracture. In the analysis, the smallest reduction in CTX appeared to be 30%, by interpolation of the data provided in figure 2.[11] The relationship between reduction in CTX and fracture risk appears broadly linear. Some of the studies included data from patients where CTX had not been measured fasting, first thing in the morning, and is thus less reliable.

In the IMPACT study – an open-label study of 2302 osteoporotic post-menopausal women who received 5mg risedronate daily for one year – 83% of treated women had suppressed their serum CTX beyond the LSC (given then as 30%) at 10 weeks; non-vertebral fracture incidence was higher (4.3%) amongst those who did not suppress their CTX by >30%, compared to those who did (1.7%).[12]

1.2.5 WHAT IS THE EVIDENCE TO SUPPORT A THRESHOLD OF CTX THAT INDICATES AN EFFECT THAT INFORMS SELECTION OF A DOSE FOR THE REMAINDER OF THE STUDY?

The proposed threshold for "efficacy" in the determination of Optimal Biologic Dose (OBD) was set at a reduction in CTX of 30% to reflect our interpretation of preclinical data in relevant animal models and data from adult studies of osteoporosis, as data from adults with OI in respect of CTX is lacking. The preclinical data from 2 different model systems, one of which is milder, both indicated that a reduction in CTX was associated with a substantial increase in bone mass. In the more severe model system ($crtap^{-/-}$), the reduction in CTX associated with treatment with an anti TGFβ antibody for 8 weeks was 25% and was associated with almost complete restoration of vertebral bone mass (235% increase) and architecture.[3] In our studies of the milder model (OIM) treated with losartan 0.6g/l in drinking water (equivalent to 48mg/kg for the mice), the reduction in CTX was 40% and associated with a 6 fold increase in bone mass compared to placebo. This dose was chosen as it was the same as that reported for a number of studies focusing on the effects of losartan on muscle outcomes.[13] Depending on the modelling approach used to "translate" mouse to human doses, such a dose could equate to a dose within the range used to treat hypertension, but might also substantially exceed it. Calculation based on surface area scaling as per a recent article from Nair and Jacobs[14] suggests this dose equates to 4.4mg/kg in humans, more than three times the maximum dose used in clinical practice in humans. Other studies of the antihypertensive effect of losartan in mice have used a lower dose of 10mg/kg, which

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would scale to 0.92mg/kg. There is thus significant uncertainty regarding both inter-species scaling and ascertaining a dose to give sustained long-term decrease in CTX which is associated with improved bone density whilst minimising side effects.[15]

Although we lack data for serum CTX in adults with mild OI, as stated above, the overall reduction in bone resorption activity in children as assessed using urine NTX was just under 30% at 3 months and just over 20% after 6 months treatment with risedronate in the POISE study[1] (interpolated from figure 4 in the reference), and these reductions were associated with both increased bone mass and fracture risk reduction.

The absolute determination of a change in CTX being predictive of anti-fracture efficacy in adolescents and adults with OI who typically fracture only once every 2 years would require a much larger study that is unlikely to be completed within the time and budget available. In terms of improving measurement precision, some of the published data, including that in the meta-analysis of the relationship of bone turnover markers with fracture,[12] included CTX measurements that were made at later times in the day, presumably in a non-fasting state. We will ensure that all samples in the MOI-A study are taken between 7.30 and 09.00AM as described in the study protocol.

It is possible that using bone densitometry of the lumber spine as an efficacy outcome would yield informative data, but it is difficult to say that it would help in terms of determination of an "optimal" dose, given the need for a longer period on a given dose of treatment to show least significant change (LSC). We will use change in CTX to determine the response to losartan of adolescents and adults with OI. Each individual will thus act as their own control. The shape of the response curve as dose is increased will enable better understanding of the pharmacodynamics in this setting.

1.2.6 SECONDARY CLINICAL OBJECTIVES

The secondary clinical objectives are to determine the changes in proxy efficacy outcomes for bone (turn over, mass, architecture and strength) using blood test, High Resolution peripheral Quantitative CT (HRpQCT) and Dual Energy X-ray Absorptiometry (DXA) and muscle (strength) using the "Timed Up and Go" test, and determine changes in quality of life using a validated disease-specific tool (OI-QoL).

At the recent UK and Ireland Brittle Bone Society patient group meeting, Dundee, August 2018, a convenience sample of approximately 100 individuals of largely UK/European origin, 80 with OI, were separated into groups of 8-10, and asked to document their thoughts surrounding research priorities in OI, highlighting the themes that they felt should be at the forefront of OI research. 146 thoughts and opinions were documented; 14 main themes were uncovered, with some subthemes. The most common theme was around treatment and management (n=32), then pain (n=19), psychosocial effects and quality of life (n=17), effects of OI on soft tissues, including muscles and hypermobility (n=16), genetics and diagnosis (n=15) heart and lung issues (n=9) sleep and fatigue (n=8) with all other themes mentioned less often.

1.2.7 STUDY OBJECTIVES SELECTION SUMMARY

We have given careful consideration to the selection of both the primary and secondary objectives, in particular with regard to the relationship of the selected biomarkers with the desired outcome of fracture risk reduction as well as considering the short period of the study.

In constructing this proposal we have considered patient priorities for research, and engaged with people with OI and patient group representatives in the development of this protocol. We expect continued patient and public involvement at every stage of this endeavour.

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2.0 AIMS AND OBJECTIVES

Primary Objective:

- To establish the effective dose of losartan in 30 older adolescents and adults aged 16 years and above with OI, based on maximal reduction in the bone resorption marker carboxy-terminal crosslink of type I collagen telopeptide (CTX)

Primary Endpoint:

- Percentage change in CTX over the 24-week period of the study

Secondary Objectives:

- To determine the changes in proxy efficacy outcomes for bone (turn over, mass, architecture and strength) using blood test, High Resolution peripheral Quantitative CT (HRpQCT), Dual Energy X-ray Absorptiometry (DXA) and muscle (strength) using the "Timed Up and Go" test
- To determine changes in quality of life using a validated disease-specific tool (OI-QoL)

Secondary Endpoints:

- Percentage change in CTX at week 8
- Percentage change in TGFβ & P1NP at week 8
- Percentage change in TGFβ & P1NP over the 24 week period of the study
- Change in DXA LSaBMD
- Change in radial and tibial total vBMD by HRpQCT
- Change in Timed Up and Go test
- Change in OI QoL

3.0 STUDY DESIGN

3.1 TRIAL DESIGN

This is a Phase 2/pilot, open label dose escalating study. Final dose is randomly assigned. This study aims to identify the "effective" dose for losartan in this population to inform the design of such a pivotal study.

Note: the scope of the study is limited by time and resource and there is no intention to undertake a pivotal study with fracture incidence as the outcome.

3.2 STUDY COHORTS

Adolescents and adults [16 years and above] with Osteogenesis Imperfecta

3.3 SAMPLE SIZE

The study sample size is 30. This is a pragmatic sample size given the rarity of OI. No conventional power calculations have been performed, see section 9.1. Up to 6 participants will be replaced following early withdrawal events allowing for a 20% attrition rate.

3.4 SITES

UK sites: Sheffield Children's Hospitals, Sheffield Teaching Hospitals Northern General (STH NGH) and Royal National Orthopaedic Hospital Stanmore

Italian sites: Bologna, Verona, Rome

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3.5 STUDY DURATION

Excluding screening period, the study treatment period is 24 weeks.

3.6 STUDY TREATMENTS

Thirty participants will be randomised at baseline to one of three “final doses” - 25, 50 or 75mg once daily. All participants will start on 25mg once daily. Those assigned to higher “final doses'' will increase in 25mg once daily increments on Day 8 and Day 15 following safety assessments to develop a final estimate of OBD.

3.7 STUDY SCHEDULE

The study schedule is in the intervention table 1 on page 28

4.0 RECRUITMENT PROCESS

Recruitment will be competitive across all study UK and Italian sites but site target recruitment rates will be agreed in the set-up period based on the number of potential participants with OI. Underperformance will be monitored and managed via the HHTU project team with additional support offered through the country-specific coordinating centre as required.

In the UK, recruitment will take place in three clinical sites and who will recruit an estimated target of 15 but may be more or less depending on the recruitment rate in both countries.
All participating sites will identify and recruit eligible participants ensuring adherence to time and target, and will either directly undertake, or have access to the facilities required to undertake, the specified investigations.

Total study recruitment targets will be approximately 2 participants per month across all UK and Italian sites. To achieve these metrics, the following monthly performance minimums are: 8 participants contacted and invited, 4 provided informed consent and attend screening; 2-3 pass screening to attend first visit. The eligibility criteria have been designed to be broad enough without compromising participant selection. The recruitment strategy allows for replacement of up to 6 participant withdrawals within the specified timeframe.

The use of a web-based database and randomisation system, supplied by HHTU, will enable study recruitment to be monitored centrally and reported to the trial oversight committees. If sites are not meeting predicted recruitment rates then in mitigation we will work with them and our patient groups and organisations to identify issues and amend recruitment strategies or consider the addition of further sites if required.

4.1 PARTICIPANT IDENTIFICIATION AND APPROACH

Participants will be recruited from the patient populations attending for treatment of OI at the participating sites. Combined, the participating sites have a large OI patient population.
Only members of the clinical team involved in patient care will access their records for the purposes of identification. Any approach to discuss potential participation will be undertaken by a member of the clinical team in the first instance. This approach will take place in clinic or by invitation letter if the clinic appointment is more than three months beyond the commencement date of the project.
The clinical team, with patient permission will refer potential participants to the site PI and research team who will confirm their potential to meet eligibility criteria (see section 4.4) by searching any relevant database of patients attending hospital with OI, or from personal knowledge of patients. Note that full eligibility will be confirmed once informed consent has been taken so that additional screening interventions can be undertaken (see section 4.2).

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If potentially eligible, the site PI and team will send them a Participant Information Sheet [PIS] containing details of the study.
The site study team will provide the Participant Information Sheets (PIS), consent forms in English. Translation of the PIS into other languages is not feasible given the diverse languages that potential patients may speak. However, where a non-English speaker is identified as eligible for the study and there is sufficient time, translated written information [PIS and Informed Consent Forms] will be provided where possible and practicable (we have access to translational facilities through the REMEDI4AL consortium). In addition, or if translated documents are not available, a local NHS Trust interpreter may be requested by the potential participant to attend study discussions and informed consent visits with the participant.
Italian sites will have a translated version of the master PIS approved by the Italian regulatory authorities.

4.2 INFORMED CONSENT

The site PIs will invite potentially eligible participants to provide Informed Consent.
Informed consent will be obtained following discussion of the study with the potential participant. The role of the participant and the procedures involved will be explained in detail. A PIS with contact details of the researcher and any research nurse or other local team members will be provided.
At least a day will be given for the potential participant to make the decision on whether to take part or not. It will be made very clear to the potential participants that they do not have to participate in the study if they don't wish to and that whatever they decide to do, it will not affect their clinical care one way or the other. Researchers will ensure that participants understand that they are free to withdraw from the study at any time. However, we will ask participants to consent to ongoing safety reporting after withdrawal for regulatory purposes and to ensure that they are aware that their data will be used in analysis up to the point of withdrawal.

4.3 SCREENING

The time and event table, details the study screening procedures (see section 6).
Written informed consent to enter into the study must be obtained from participants after explanation of the aims, methods, benefits and potential hazards of the trial and **BEFORE** any study-specific procedures are performed or any blood is taken for the study. The only procedures that may be performed in advance of written informed consent being obtained are those that would be performed on all patients in the same situation as a usual standard of care.
Informed consent will be obtained prior to collection of information necessary to evaluate patient eligibility.
Screening against the study eligibility criteria will be undertaken by the clinical site PIs and research nurses.
Patients will be screened using the history of their OI, supported by any available clinical correspondence according to usual standard of care.

Eligibility checks include:

- Blood tests: Full Blood Count (haemoglobin, haematocrit, red blood cell count, white blood cell count, platelets, neutrophils, eosinophils, basophils, lymphocytes and monocytes), Urea & Electrolytes and Liver Function Tests.
- Urine Pregnancy test for women of child bearing potential (WOCBP).

4.4 ELIGIBILITY

4.4.1 INCLUSION CRITERIA

- Age 16 years and above
- Diagnosed with osteogenesis imperfecta (any type)

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- Prior treatment with up to and including 6 weeks of oral bisphosphonate therapy is allowed provided there has been a 12 month washout period since the last dose of treatment.
- Prior treatment with a single dose of an intravenous bisphosphonate is allowed provided there has been an 18 month washout period since the treatment was given.
- Prior treatment with a single dose of denosumab is allowed provided there has been a 12 month washout period since the treatment was given.
- A women of childbearing potential (WOCBP) who agrees to use an effective method of contraception from point of signing the informed consent throughout the study.
- Agreed not to participate in another interventional research project during their involvement in this study.
- Not taking prohibited concomitant medications, listed in exclusion criteria.
- Any other contraindication that makes the patient unsuitable to take part in the study in the opinion of the investigator.

The inclusion criteria are based upon the following considerations:
1. Age 16 years and above for the following reasons:

a. The participant needs to be able to report on feelings of dizziness or unsteadiness that might occur following losartan administration.
b. The patient group input was that it was appropriate to include participants within this age bracket.
c. We anticipate future studies in children and will use safety data from this study to help inform dose considerations in children.

2. Diagnosed with OI based on established clinical criteria. This is the disease group we wish to target, where preclinical data suggest that the intervention may have a beneficial effect in reducing bone turnover in OI, and improving muscle function in multiple sarcopenic or myopathic models. OI is a clinical diagnosis based on the presence of fragility fractures as well as other clinical findings including, but not limited to, hypermobility, musculoskeletal pain, sarcopenia, blue sclerae and reduced stature.

3. Losartan is an AT1 receptor blocker and can have teratogenic effects if administered in early pregnancy, hence the need for female participants of child-bearing age/potential to take contraceptive measures for the period of the study.

4. Involvement in another interventional project is not generally permitted as the effect of one intervention can interfere with the assessment of the other.

5. Avoidance of other drugs that can contribute to known side effects or issues with losartan – e.g. including but not restricted to other antihypertensive agents, potassium-retaining or potassium-elevating drugs.

4.4.2 EXCLUSION CRITERIA

- Current use of losartan
- Prior use of losartan within preceding 6 month to enrolment
- Presence of other chronic illnesses including renal failure likely to affect bone metabolism or structure
- Known severe hypotension resulting in dizziness, fainting or headaches
- Hyperkalaemia
- Current medication that increases potassium retention, or may increase potassium levels, such as potassium-retaining diuretics
- Current medication with lithium.
- Current medication with other substances which may induce hypotension

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- Currently taking oral bisphosphonates or intravenous bisphosphonates
- Prior treatment with more than 6 weeks oral bisphosphonates treatment
- Prior treatment with more than a single dose of intravenous bisphosphonate
- Prior treatment with more than one dose of denosumab
- Recent (last 12 months) or current treatment likely to affect bone – this does not include inhaled or intermittent oral therapy with steroids for asthma (no more than three months of oral steroids in previous 12 months)
- Severe Hepatic impairment
- Renal impairment (GFR <60ml/min/m2) if treated with aliskiren-containing products
- Diabetes mellitus if treated with aliskiren-containing products
- Cardiac failure treated with diuretics
- Pregnancy or lactation
- Known hypersensitivity to losartan or any of the excipients
- Recent fracture in the prior 6 months to enrolment

The exclusion criteria are based upon the following considerations:

1. Current use of losartan
2. Prior use of losartan within preceding 6 month to enrolment
3. Presence of other chronic illnesses likely to affect bone metabolism or structure. Although unusual, other chronic diseases can be present in OI; given the limited objectives for the study in terms of defining OBD for losartan and identifying the size of proxy responses, we wish to reduce the likelihood of confounding any of the outcomes.
4. Hypotension is a potential complication of treatment with losartan; symptomatic hypotension is likely to be worsened with treatment.
5. Hyperkalaemia occurs in some individuals treated with losartan; a baseline potassium above the upper limit of the age and gender-specific reference range is a dose-reduction criterion, hence a patient should not start treatment if they already meet this criterion.
6. Not treated with bisphosphonates or denosumab, or with minimal prior treatment. The primary clinical outcome for the study is the determination of the “effective dose” of losartan, assessed by the reduction in the bone resorption marker CTX. Bisphosphonates and denosumab act by reducing bone resorption, and thus change in CTX may be affected by a prolonged period of prior treatment occurring in the recent past. As things stand, we have identified over 150 eligible participants who are completely naïve to treatment, so we may not have to recruit any that have had prior treatment.
7. Medications affecting bone could also affect the CTX response to treatment with losartan, either increasing CTX, or reducing it within the time period of the assessments.
8. Severe hepatic impairment as per Summary of Product Characteristics (SmPC).
9. Significant renal impairment requires careful monitoring as per SmPC.
10. Cardiac failure requiring use of diuretics, requires careful monitoring as per SmPC.
11. Pregnancy is an absolute contraindication to the use of losartan; lactation alters bone turnover.
12. Exposure of participants to a substance known to result in a hypersensitivity reaction is clearly inappropriate.
13. Recent fractures can elevate CTX levels for up to 6 months.

OI severity is not a specific inclusion or exclusion criterion, but naivety/very low exposure to prior bisphosphonate exposure will mean that most patients will fall at the milder end of the spectrum of severity.

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4.5 CONCOMITANT MEDICATIONS

The concomitant use of losartan potassium with aliskiren-containing products is contraindicated in patients with diabetes mellitus or renal impairment (GFR < 60 ml/min/1.73 m^2).

Other medications not permitted within the study are specified within the participants eligibility criteria; no rescue therapy should be required – cessation of therapy will result in clearance of losartan and its active metabolite within 48 hours.

4.6 WITHDRAWAL OF PARTICIPANTS

The right of a participant to refuse participation without giving a reason must be respected. The participant must remain free to withdraw at any time from the study without giving reasons and without prejudicing his/her further treatment. Although not obliged to give a reason for discontinuing their study treatment, a reasonable effort should be made to establish this reason to inform study implementation, whilst remaining fully respectful of the participant's rights. Where a participant is required to re-consent or new information is required to be provided to a participant it is the responsibility of the PI to ensure this is done in a timely manner and according to any timelines requested by the HHTU.

If a participant chooses to discontinue their study treatment, up to 6 participants will be replaced to ensure sufficient data for analysis. Sites will inform HHTU of the withdrawal in the study database and via the study withdrawal visit Case Report Form (CRF). Data already collected will be kept and included in analyses according to the intention-to-treat (ITT) principle for all participants who stop follow up early. Data pertaining to safety will continue to be collected for regulatory reporting purposes and will be included in any safety analysis.

For participants withdrawing from the study, they will continue to receive treatment for their OI in accordance with local standards of care. Before any participant undertakes any study activity, written informed consent will be obtained from participants prior to study enrolment.

After the participant has enrolled, the study clinician remains free to offer and provide alternative treatment to that specified in the protocol, at any stage, if s/he feels it to be in the best interest of the participant. The reasons for doing so must be recorded.

4.6.1 PROTOCOL TREATMENT DISCONTINUATIONS

In consenting to the study, participants are consenting to study treatments and data collection. However, an individual participant may stop treatment early or be stopped early for any of the following reasons:

- Unacceptable treatment toxicity or adverse event
- Inter-current illness that prevents further treatment
- Any change in the participant's condition that in the clinician's opinion justifies the discontinuation of treatment
- Pregnancy
- Withdrawal of consent for treatment by the participant

See section 7.9. and Flow diagram 1 (page 34) on dose modification and discontinuation criteria.

4.7 PARTICIPANT REPLACEMENT

We have allowed for replacement of up to 6 participants who withdraw from the study based upon 20% attrition rate.

4.8 CONTRACEPTIVE GUIDANCE AND PREGNANCY

A Woman of Childbearing Potential (WOCBP) is considered fertile following menarche and until becoming post-menopausal unless permanently sterile.

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A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.

Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

Women of childbearing potential (WOCBP) participants are eligible to participate if they agree to use an effective method of contraception as listed below, from point of signing the informed consent throughout the study.

● Combined (estrogen- and progestogen- containing) hormonal contraception (Oral, Intravaginal, Transdermal or Injectable)
● Progestogen-only hormonal contraception (Oral or Injectable)
● Progestogen- only contraceptive implant
● Intrauterine hormone-releasing system (IUS)
● Intrauterine device (IUD)
● Bilateral tubal occlusion
● Vasectomized partner provided that the vasectomised partner is the sole sexual partner of the WOCBP.
● Sexual abstinence only if is the preferred and usual lifestyle of the subject.

Urine pregnancy test for women of child bearing potential (WOCBP) will be performed at the screening and baseline visits and subsequently every 4 weeks at the scheduled visits. If a patient is unable to provide a urine sample we will carry out a serum pregnancy test.

If a participant become pregnant

1. Investigator will attempt to collect pregnancy information on study participant who becomes pregnant while participating and will inform the HHTU and the sponsor within 2 weeks of learning of the pregnancy.
2. Pregnancy will also be followed to determine the outcome. Information on the status of the mother and child will be forwarded to HHTU. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of foetal status (presence or absence of anomalies) or indication for procedure.

5.0 ENROLMENT AND DOSE ALLOCATION

All participants will be enrolled into the study REDCap database immediately after consent to generate a pseudonymised Subject ID Number. This number will be used on all study documentation going forward.

5.1 THE RANDOMISATION SCHEME

All 30 participants will be randomised sequentially and the responsible statistician will prepare a randomisation schedule using the block randomisation with variable block sizes in a 1:1:1 ratio so that 10 participants will be randomised to each final dose arm i.e 10 randomised to final dose of 25mg, 10 participants to 50mg and 10 participants to 75mg.

Randomisation will be completed via the REDCap Cloud (RCC) online system provided by the HHTU. Full details of the randomisation scheme is not included in the study protocol as knowledge of these details might

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undermine randomisation by facilitating deciphering of the allocation sequence. Instead, this specific information will be provided in a separate document with restricted access.
In the event of the RCC randomisation system being unavailable a contingency randomisation plan will be in place, detailed in the Data Management Plan.

5.2 METHOD OF IMPLEMENTING THE ALLOCATION SEQUENCE

Once a site is permitted to proceed with randomisation for a consented participant, authorised study staff with delegated responsibility for randomisation will follow the instructions in the latest study REDCap Cloud (RCC) User Manual, held in the Investigator Site File. This will involve logging onto the secure online randomisation system (RCC) administered by HHTU. RCC user accounts will be set up for delegated site staff by HHTU once all the necessary study documentation and approvals for participation in the study have been received. Randomisation will not be activated at individual sites until the sponsor green light approval has been confirmed.
The online randomisation system will include an eligibility check before allowing randomisation to be completed. HHTU will receive an alert with confirmation of the site randomisation and assigned Subject ID number. The participant's Subject ID number should be added to the site screening log and participant register. The Subject ID number will be entered on all participant study documents and future correspondence from that point forward throughout the study. No other patient identifier will be used.
The online randomisation system will not automatically generate a study prescription form.

5.3 AVOIDING BIAS

Given that this is a dose escalation study, both the participant and the investigators will be aware of the dose that the participant receives.

6.0 STUDY INTERVENTIONS

See Table 1 on page 28 for a summary of the study intervention schedule.

6.1 SCREENING VISIT

The screening visit will take place between Day-28 and Day 0 in order to confirm eligibility and will include the following interventions: informed consent, medical history, fracture history, physical/clinical exam, BMI [weight/height], vital signs [TPR, BP, O_2 saturations], urine pregnancy test for women of child bearing potential (WOCBP), blood test [FBC, U&Es, LFTs]. A GP letter will be sent after consent and before randomisation so that the GP will have been informed before the participant takes their first dose of study medication.

6.2 BASELINE AND FIRST DOSE OF STUDY IMP [SITE VISIT]

On Day 1, once the participant has completed the baseline assessments, they will be randomised and will take their first dose of study IMP whilst in the sites. In order to monitor vital signs and check for adverse events and reactions this visit will take up to 4-6 hours. Vital signs will be checked.
Other baseline investigations include:

- **HRpQCT scan radius and tibia**: High resolution peripheral quantitative computed tomography (HRpQCT) scan radius and tibia will be undertaken at Sheffield Teaching Hospitals Northern General (STH NGH) Site; participants (and a carer if needed) will be offered one night's accommodation and subsistence to travel to Sheffield for the purposes of the scans. The scan must be completed between the baseline visit and Day 7 visit. Participants sit in a special chair and place either their wrist or ankle into a cylindrical aperture, keeping it very still for the duration of the scan which is around 3-4 minutes. A supportive splint is provided to help with this.

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- **DXA LS and Hip**: Dual x-ray absorptiometry (DXA) Lumbar Spine and Hip scans are a standard way of assessing bone density in both children and adults; participants lie on a couch and the scan arm passes above them to provide a quantitative assessment of bone size and mass. Scans take about 1 minute each. They will be done at the same time as the HRpQCT scans at STH NGH. The scan can be completed between the baseline visit and Day 7 visit.
- **"Timed up and go" test:** An assessment of participant to determine fall risk and measure the progress of balance, sit to stand and walking. Assessment takes a maximum of 2 minutes each.
- **Pubertal stage assessment:** Pubertal status will be assessed on patients under 21 years old.
- **OI Quality of Life (QoL)**: Validated questionnaire.
- **Blood tests:** Full Blood Count (FBC), Clinical Chemistry (U&Es), Liver Function Tests (LFTs)
- **Fasting blood tests**: CTX, Losartan, TGFβ, P1NP
- **Bone Profile blood tests:** 25 OHD, PTH

The HRpQCT and DXA scans requires exposures to ionising radiation that have been assessed by IRMER medical physics based at Sheffield Teaching Hospital on behalf on the sponsor. Some/all of the exposures required by the study are additional to routine clinical care. The total protocol dose is 0.064 mSv. This is equivalent to about 2 weeks 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 less than 0.001 %, which is low. For comparison, the natural lifetime cancer incidence in the general population is about 50%.

Participants and one parent/guardian will be offered food and accommodation in a local hotel on the evenings before or after of their scan visits if required to help with travel arrangements.
On site visits participants and one parent/guardian will be offered refreshments after fasting blood test and study intervention if required.

6.3 DOSE ESCALATION / MODIFICATION VISITS [SITE VISITS]

The study visits at Week 1, 2, 3, 4 & 5 will be clinic visits. The research team will complete the visit assessment including dose escalation in line with the dose escalation algorithm and assigned randomisation group, or modified in line with safety checks conducted at the week 1, 2, 3, 4 & 5 visits. See section 7.9. and Flow diagram 1 (page 34 for more detail on the dose escalation / modification process.

6.4 SITE VISITS

Week 8, 16, 24 and early withdrawal visit will all be conducted at the Clinical Research Facility.

6.5 SITE/HOME VISITS

Week 12, 20 may be done via home visits or clinic.

6.6 TELEPHONE VISIT

Week 6 will be a telephone visit for AE and concomitant medication checks only.

6.7 FOLLOW UP VISITS

There are no follow up visits after week 24.

6.8 FASTING BLOOD TESTS

There are fasting blood tests at Day 1, Weeks 1, 4, 8, 24 and early withdrawal visit to take into consideration when scheduling these visits.
See section 8 for further detail on sample management.

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TABLE 1: STUDY INTERVENTION SCHEDULE TABLE

PART 1: Visit and site:	Pre-dose Screening	Baseline	4 hours post dose	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 8	Week 12	Week 16	Week 20	Week 24	Unscheduled Visit	Early withdrawal
	D-28 to D0	D1	D1	D7	D14	D21	D28	D35	D42	D56	D84	D112	D140	D168		1-3 ALD
Permitted Visit Window	-28 D	0	0	0	0	0	0	0	0	-1 D	-2 D	-2 D	-2 D	-2 D		
Overnight stays offered		2												1		
Site visit	x	x	x	x	x	x	x	x		x		x		x	x	x
Site/Home visit											x		x			
Telephone call									x							
Informed consent	x	Re-check														
Eligibility criteria	x	x														
Medical history	x															
Fracture history	x															
Pubertal stage assessment		x														
Fracture incidence		x					x			x	x	x	x	x		x
Clinical/physical examination	x	x								x				x		x
Height/Weight (BMI)	x	x								x				x		
Observations; TPR, BP, O_2 Sat	x	x	x	x	x	x	x	x		x	x	x	x	x	x	x
Urine for pregnancy test (Women of Child Bearing Age)	x	x					x			x	x	x	x	x		x
Randomisation (final dose assignment)		x														
Drug administration training		x		x	x	x	x								x	
Dose modification assessment				x	x	x	x	x		x		x			x	
Dispensing		x		x	x	X	X	x		X		x			x	
First administration of increased dose				D8	D15											
Drug accountability				X	X	X	X			X		x		X		x
HRpQCT scan radius and tibia		x*+5												x*+10		after W 12*+10
DXA LS and Hip		x*+5												x*+10		after W 12*+10
"Timed up and go" test		x								x				x		after W 12
OI Quality of life tool, face-to-face interview		x								x		x		x		x
Clinical laboratory: FBC, U&Es, LFTs, Urine dipstick	x	x		x	x	x	x	x		x		x		x	x	x
Fasting blood sample: CTX, TGFβ, P1NP		x		x			x			x				x		x
losartan		x					x			x				x		x
Bone profile, 25OHD, PTH		x								x				x		x
Adverse events		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant medications	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x

a. Participant's safety assessed for dose escalation/modification until maximum allocated dose achieved. Principal Investigator must confirm if patient can proceed to next available dose for patient to start on the following days – D8, D15.

b. Participants who decide to leave the study or who are withdrawn will be asked to attend an unscheduled early withdrawal visit to assess patient safety and collect surplus drug supplies. Schedule after 1 to3 days after last dose (ALD). If a participant decided to withdrawn in or after week 12 would be optional to do HRpQCT scan radius and tibia, DXA LS and Hip and "Timed up and go" test. For earlier withdrawal don't need to repeat these tests.

* The scans at the baseline visit can be completed at the same day of the visits or within 5 days after the visit. The scans for the final visit and withdrawal visit after 12 weeks can be completed at the same day of the visits or within 10 days after the visits. Participant and one parent/guardian if required will be offered food and accommodation in a local hotel to help with travel arrangements.

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7.0 IMP MANAGEMENT

7.1 STUDY MEDICATION

The study IMP will be losartan potassium 25mg film-coated tablets supplied by the Organon Pharma (UK) Limited. Marketing Authorisation (PL 00025/0336) holder Organon Pharma (UK) Limited, The Hewett Building, 14 Hewett Street, London, EC2A 3NP, UK.

Losartan is only available as a tablet for oral administration and comes in blister packs of 28 tablets (2x14).

Full product information can be seen in the SmPC.

7.2 IMP BENEFITS

- Essential hypertension in adults and in children and adolescents 6-18 years of age.
- Renal disease in adult patients with hypertension and type 2 diabetes mellitus with proteinuria ≥ 0.5 g/day as part of an antihypertensive treatment.
- Chronic heart failure in adult patients when treatment with Angiotensin converting enzyme (ACE) inhibitors is not considered suitable due to incompatibility, especially cough, or contraindication. Patients with heart failure who have been stabilised with an ACE inhibitor should not be switched to losartan. The patients should have a left ventricular ejection fraction ≤ 40% and should be clinically stable and on an established treatment regimen for chronic heart failure.
- Reduction in the risk of stroke in adult hypertensive patients with left ventricular hypertrophy documented by ECG.

7.3 IMP CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients
- 2nd and 3rd trimester of pregnancy
- Severe hepatic impairment

Losartan has a number of side effects, as listed below:

Common (may affect up to 1 in 10 people):

Dizziness, low blood pressure, (especially after excessive loss of water from the body within blood vessels e.g. in patients with severe heart failure or under treatment with high dose diuretics), dose-related orthostatic effects such as lowering of blood pressure appearing when rising from lying or sitting position, debility, fatigue, too little sugar in the blood (hypoglycaemia), too much potassium in the blood (hyperkalaemia), changes in kidney function (may be reversible upon discontinuation of treatment) including kidney failure, reduced number of red blood cells (anaemia), increase in blood urea, serum creatinine and serum potassium in patients with heart failure.

Uncommon (may affect up to 1 in 100 people):

Somnolence, headache, sleep disorders, feeling of increased heart rate (palpitations), severe chest pain (angina pectoris), shortness of breath (dyspnoea), abdominal pain, severe constipation, diarrhoea, nausea, vomiting, hives (urticaria), itching (pruritus), rash, localised swelling (oedema), cough.

Rare (may affect up to 1 in 1,000 people):

Hypersensitivity, angioedema, inflammation of blood vessels (vasculitis including Henoch-Schönlein purpura), numbness or tingling sensation (paraesthesia), fainting (syncope), very rapid and irregular heartbeat (atrial fibrillation), brain attack (stroke) (rapidly developing loss of brain function(s)), inflammation of the liver (hepatitis), elevated blood alanine aminotransferase (ALT) levels, usually resolved upon discontinuation of treatment.

Not known (frequency cannot be estimated from available data):

Reduced number of thrombocytes, migraine, liver function abnormalities, muscle and joint pain, flu-like symptoms, back pain and urinary tract infection. Increased sensitivity to the sun (photosensitivity), unexplained muscle pain with dark (tea-coloured) urine (rhabdomyolysis), impotence, inflammation of the

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pancreas (pancreatitis), low levels of sodium in the blood (hyponatraemia), depression, generally feeling unwell (malaise), ringing, buzzing, roaring, or clicking in the ears (tinnitus), disturbed taste (dysgeusia).

7.4 IMP REFERENCE SAFETY INFORMATION / SUMMARY OF PRODUCT CHARACTERISTICS (SMPC)

The Summary of Product Characteristics (SmPC) will be used as the Reference Safety Information (RSI). The current MHRA approved version will be clearly listed in the pharmacovigilance section of the site file.
The study will replace the RSI with updated versions as appropriate during the study period, with new versions being formally reviewed as part of an updated risk assessment and implemented after a substantial amendment has been approved by the MHRA.

7.5 IMP STORAGE AND SUPPLY

The IMP will be provided by Organon Pharma (UK) Limited (Marketing Authorisation Number: PL 00025/0336) through normal routes from a single supplier.
Losartan tablets have a shelf life in excess of 2 years, well beyond the period of the study. Storage is at room temperature.
This is an open label study and treatment allocation will not be concealed from the investigator, patients, the site research team, HHTU team and pharmacists. IMP will be supplied to site pharmacy units from routine NHS Trust stocks as blister packs. IMP supplies will be sourced from local site pharmacies in order to distribute timely and sufficient quantities of losartan in each dose group. The IMP will be supplied in 28 tablets (2x14 blister strips) in boxes. Each IMP blister box will be relabelled by the site pharmacy team before dispensing to the participant. Each box will have the Subject ID Number and a unique identifier (i.e. a Kit Number) in order to record drug accountability. IMP boxes will be dispensed from site pharmacy units according to the study prescription and dispensing logs.
IMP will be held in the Clinical Trials area of each site's pharmacy and will be relabelled for study use at each dispensing.
Further details are provided in the Study Pharmacy Manual.

7.6 IMP PREPARATION, DISPENSING AND LABELLING

This will be undertaken at each site pharmacy with relabelling of the IMP according to the randomised dose that the patient is assigned to. New relabelled IMP will be provided at each dose change. Study IMP will be stored and dispensed by participating site pharmacies in accordance with Good Clinical Practice.
Further details are provided in the Study Pharmacy Manual.

7.7 IMP DOSING ADMINISTRATION, DOSAGE AND TREATMENT PERIOD

Study IMP will be administered once daily by the participant, or if necessary in the adolescent cohort, by a parent. The first dose will be taken whilst in the Clinical Research Facility on Day 1 to monitor for Adverse Events and Reactions. The treatment will not continue beyond the period of the study as this is a pilot/demonstrator study to see whether we get a positive response in a proxy biomarker. If that positive response is seen then we will undertake a large-scale phase 3 trial with a fracture as the outcome.
Further details are provided in the Study Pharmacy Manual.

7.8 BATCH RECALL

In the event of a required batch recall, the site pharmacy unit will check against the dispensing list for any affected IMP, and patients will be contacted to return the medication.
Further details are provided in the Study Pharmacy Manual.

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7.9 IMP DOSE MODIFICATIONS

Dose modifications occur at specific timepoints in the study intervention. However, participant doses may escalate or reduce depending on dose modification safety assessments. A safety assessment will consist of both a serum potassium check (blood test) and a hypotension assessment (blood pressure and symptom check). Both have the potential to modify the dosing schedule and both will be conducted before a decision to dose escalate it taken.

Serum potassium checks: A blood sample will be taken to check serum potassium levels. A raised serum potassium is defined as raised beyond the Upper Level of Normal (ULN):
Note: 'Normal' serum potassium results can vary slightly according to patient age, gender and laboratory depending on the assay used for testing blood samples. Each site pathology department responsible for testing routine blood samples will provide laboratory ranges for age and gender-related potassium levels during study set up. This will ensure serum potassium results are measured against the specific assay that was used. A ULN result will be specific to each laboratory.

Hypotension assessment: Blood pressure and symptom assessments will be conducted to check for hypotension. An unacceptable hypotension assessment is defined as: 'Persistent' symptoms of continuous dizziness and fainting that persists and is present one week later at the next study visit.

7.9.1 IMP DOSE ESCALATION SCHEDULE

All participants will be randomised at Day 1 to their final dose allocation of losartan 25mg, 50mg, or 75mg once daily. However, all participants will start on the lowest dose and increase (if randomised to a higher dose) via a dose escalation pathway as described below.

Day 1 – Day 7
All participants will receive 25mg of losartan at Day 1.
On Day 7, a safety assessment check will be conducted on all participants. If either the potassium level is greater than the ULN and/or there are symptoms of persistent hypotension, the participant will be withdrawn from the study and will complete the early withdrawal visit.
If both safety assessments are within acceptable limits and the participant was randomised to either the 50mg or 75mg groups, the losartan dose will be increased to 50mg on Day 8.

Day 14 – Day 21
On Day 14, a safety assessment check will be conducted on participants taking 50mg. If both safety checks are within acceptable limits, the participant will either remain on 50mg (if randomised to that group on Day 1), or increase to 75mg (if randomised to that group on Day 1) on Day 15.
However, if either the potassium level is greater than ULN and/or there are symptoms of persistent hypotension, the dose will be reduced to 25mg. A safety assessment (for those who reduced their dose from 50mg to 25mg) will be repeated on Day 21. If the safety assessment checks are within acceptable limits they will remain on 25mg for the remainder of the study (Week 24), regardless of their original randomisation group on Day 1.
However, if either potassium level is greater than the ULN and/or there are symptoms of persistent hypotension, the participant will be withdrawn from the study and will compete the early withdrawal visit. They will be referred for further management of their raised serum potassium or persistent hypotension.

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On Day 21, a safety assessment check will be conducted on participants taking 75mg. If both safety assessment checks are within acceptable limits, the participant will remain on 75mg for the remainder of the study (week 24).
However, if either the potassium level is greater than ULN and/or the participant is experiencing persistent signs of hypotension, the dose will be reduced to 50mg. Safety checks (for those who have reduced their dose from 75mg to 50mg) will be repeated on Day 28.

Day 28 – Day 35
We will re-evaluate tolerance specifically and all participants will have a safety assessment on Day 28.
Participants taking 75mg at Day 28: If the safety assessment is acceptable, the participant will continue on 75mg to the end of the study (week 24). If the potassium level is greater than ULN and/or the participant is experiencing persistent signs of hypotension, the dose will be reduced to 50mg. Safety assessments will be conducted the following week to check if 50mg of losartan potassium and hypotension symptoms are within acceptable limits. If acceptable, the participants will continue on 50mg to the end of the study (week 24). However, if safety assessments are unacceptable, the participant may be further reduced to 25mg followed by a safety assessment check one week later. If safety assessments remain unacceptable, the participant will be withdrawn from the study and referred for further management to either their GP or their normal clinical support team.
Participants taking 50mg at Day 28: If the safety assessment is acceptable, the participant will continue on 50mg to the end of the study (week 24) regardless of their original randomisation group on Day 1. However, if safety assessments are unacceptable, the participant will be further reduced to 25mg followed by a safety assessment check one week later. If safety assessments remain unacceptable, the participant will be withdrawn from the study and referred for further management to either their GP or their normal clinical support team.
Participants taking 25mg at Day 28: If the safety assessment is acceptable, the participant will continue on 25mg to the end of the study (week 24) regardless of their original randomisation group on Day 1. However, participants who have a persistently elevated potassium or hypotension despite dose reduction to 25mg will be withdrawn from the study and referred for further management to either their GP or their normal clinical support team.

Day 42
This visit is a phone call for all participants to record any adverse event or changes on concomitant medications.

Day 56
We will re-evaluate tolerance specifically and all participants will have a safety assessment on Day 56.

Day 112 & Day 168
There will be further blood tests on Day 112 and at the end of the study on day 168.
The final visit on Day 168 the HRpQCT scan radius and tibia and DXA LS and Hip specialised scans can be repeated. The scan will be undertaken at Sheffield Teaching Hospitals Northern General (STH NGH) Site; participants (and a carer if needed) will be offered one night's accommodation and subsistence to travel to Sheffield for the purposes of the scans. The scans can be completed at the same day of the visit or within 10 days after the final visit.

Day 84 - Day 140
These visits are simply to check physical well-being so no blood tests are done. Will be either at home, or in the local centre.

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Early withdrawal Visit

Participants who decide to leave the study or who are withdrawn will be asked to attend an unscheduled early withdrawal visit to assess patient safety and collect surplus drug supplies. Schedule after 1 to 3 days after last dose (ALD). If a participant decided to withdrawn in or after week 12 would be optional to do HRpQCT scan radius and tibia, DXA LS and Hip and "Timed up and go" test. For earlier withdrawal don't need to repeat these tests. The scans will be undertaken at Sheffield Teaching Hospitals Northern General (STH NGH) Site; participants (and a carer if needed) will be offered one night's accommodation and subsistence to travel to Sheffield for the purposes of the scans. The scans can be completed at the same day of the visit or within 10 days after the visit.

Unscheduled Visit

Based on existing evidence for the general use of losartan, if serum potassium has not risen within a week of either starting or escalating the dose it is unlikely to do so. However, if at any stage there are problems with symptoms likely to be attributable to losartan, the patient is reviewed in their local centre and if necessary the dose reduced to a lower dose and the patient reassessed after 1 week - and if they are on 25mg that they are withdrawn at that stage.

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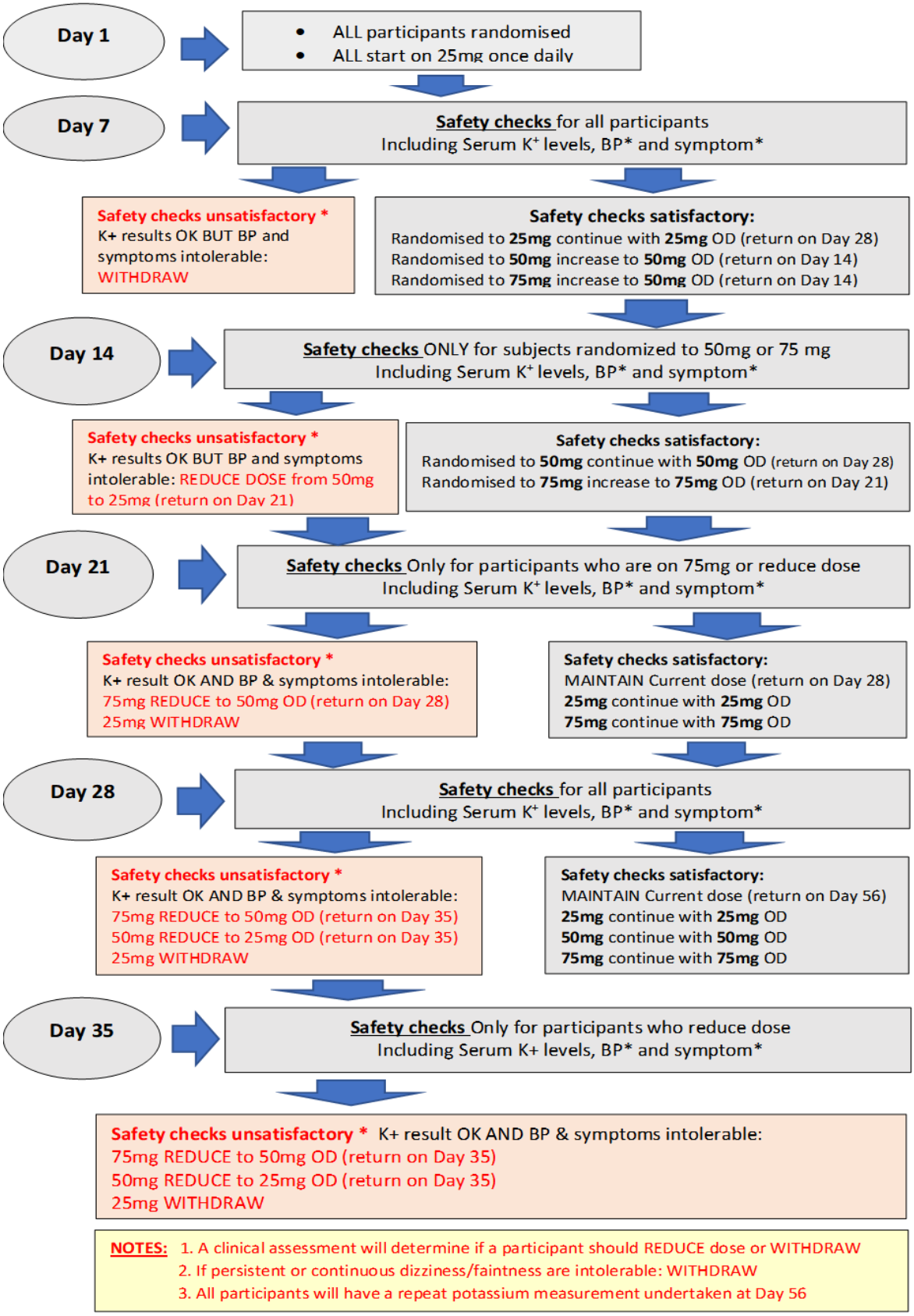
FLOW DIAGRAM 1: DOSE ESCALATION AND MODIFICATION



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7.9.2 IMP DOSE DISCONTINUATIONS

If a participant on 25mg losartan has an elevated serum potassium or persistent symptoms of hypotension one week later when it is rechecked at the next study visit, losartan will be discontinued.
If the site PI feels it is in the best interest for the participant to withdraw at any stage of the study, clinical assessment will supersede all other dose escalation and modification guidance described above.

7.10 MANAGEMENT OF KNOWN IMP RELATED HARMS

The study doses proposed are within the range specified in the SmPC for the treatment of hypertension in adolescents and adults. In participants without hypertension, doses within this range reduce diastolic blood pressure by 3-4mmHg. The treatment period is sufficient to meet the primary objective of the study, a clear reduction in CTX.

7.11 ASSESSMENT OF COMPLIANCE

A full accountability trail will be maintained from receipt of study IMP in pharmacy, up to the point of dispensing and destruction of undispensed study IMP.
The site clinical trials pharmacy team within each participating site will be delegated oversight of study IMP supplies. All study IMP must be stored in accordance with the manufacturer's instructions, and it must be kept in a locked area with restricted access to designated study personnel.
Unused dispensed study IMP will be brought to the next study visit by the participant and will be checked by the site study team. After accountability and compliance assessments have been completed, the unused study IMP will be returned to the study pharmacy team for destruction. Site will request sponsor approval before any destruction of study IMP can take place. Documentation confirming destruction will be sent to HHTU.
The importance of compliance with the study protocol will be explained to the participant during the informed consent process and confirmed again at baseline and at each follow up visit. Compliance will be optimised by informing all participants of the most commonly experienced side effects and ways of minimising these. Good relationships will be established with all study participants to maximise honest reporting of compliance.

7.12 IMP DESTRUCTION

All unused study IMP will be returned to the site study pharmacy. A study IMP destruction form will be completed and checked by HHTU before HHTU request sponsor approval for the study IMP to be destroyed. Under no circumstances can study IMP be destroyed until sponsor has given approval.

8.0 SAMPLE MANAGEMENT

This study will collect a number of different samples at different timepoints in the study. No samples will be stored beyond the study period, unless participants consented to store their samples for Future Biomedical Research. The samples required for the study are listed below. The Laboratory Manual will give further detail of the sample collection and processing.

8.1 SAFETY BLOOD SAMPLES

Full Blood Count, U&Es and Liver Function Tests are required to monitor participant safety whilst taking losartan. Blood samples will be collected at Screening, Day 1, Week 1, 2, 3, 4, 8, 16, 24 and early withdrawal visit. The blood test will be taken in standard NHS Trust venepuncture bottles up to a maximum of 20mls at each visit listed above and processed as routine samples in the pathology laboratory. They will be destroyed as soon as they have tested in line with NHS Trust policy.

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8.2 URINE SAMPLES

Urine samples will be collected for dipstick testing at Screening, Day 1, Week 1, 2, 3, 4, 8, 16, 24 and early withdrawal visit. Urine samples of approximately 25ml volume will be collected in standard NHS Trust urine collection container and will be tested and analysed by the research team in a clean testing area and then immediately discarded.

In Women of Child Bearing Age (WOBCA) the urine samples collected above will be used for pregnancy testing.

8.3 FASTING BLOOD SAMPLES

These samples will be collected for primary and secondary endpoint study measures. Fasting blood samples will be collected for CTX, TGFβ, P1NP testing at Day 1, Week 1, 4, 8 and 24 / early withdrawal visit. Losartan blood sample will be collected at Day 1, 4, 8 and 24 / early withdrawal visit. Participant must have fasted for 8 hours before the blood test is collected. The blood tests will be taken in standard NHS Trust venepuncture bottles up to a maximum of 20 mls at each visit listed above.

8.4 BONE PROFILE BLOOD TESTS

These samples will be collected for primary and secondary endpoint study measures at Day 1, Week 8, 24 / early withdrawal visit. The blood tests will be taken in standard venepuncture bottles up to a maximum of 10 mls at each visit listed above.

8.5 SAMPLE STORAGE AND PROCESSING

Specialist samples for bone turnover markers and TGFβ will be sent to the University of Sheffield Medical School bone biomarker laboratory. Losartan will be stored in the clinical sites and will be sent to a central laboratory for analysis. Other samples will be analysed locally and will be destroyed after analysis. Study laboratory manual will detail all the process and storage conditions required for all samples.

8.6 FUTURE BIOMEDICAL RESEARCH SAMPLE COLLECTION

Any unused blood samples taken for this study and not required for analysis will be stored for future research at the University of Sheffield Musculoskeletal biobank. We will ask participants to give consent for us to store their samples for Future Biomedical Research. Participation is optional and those who do not wish to consent to this element of the study may still participate in the main study.

8.7 SAMPLE DESTRUCTION

All samples will be destroyed after analysis, unless the participant consented to the biobank collection where samples will be stored for future research.

9.0 STATISTICAL ANALYSIS PLAN

9.1 SAMPLE SIZE CALCULATION

Data from a total of 30 participants (combined UK and Italy recruitment) will be used to derive a final estimate of the OBD. This will be a pragmatic sample size given the rarity of OI. No conventional power calculations have been performed.

As stated earlier in this protocol, the UK target sample size is 15. However, for statistical analysis, the combined UK and Italian recruitment target will be 30 participants. Recruitment will be competitive and UK or Italian numbers of participants may be higher or lower than stated earlier in the protocol. UK and Italian randomisation and data capture will take place via the same REDCap Cloud database.

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9.2 STATISTICAL METHODOLOGY RATIONALE

In the mouse data a "u-shaped" dose response was seen whereby at higher doses the CTX response returned to baseline. At present we are uncertain whether the exposure in the proposed study will be high enough to induce this non-monotonic dose-response shape. Using allometric scaling principles it unlikely that a "u-shaped" curve will be seen, in that the top dose (75 mg) would not be expected to give as high concentrations as the top dose in the mouse studies. However, there is no good data on inter-species scaling of CTX response to losartan, and therefore see it as a risk to only check CTX once participants are titrated to the maximum tolerated dose.

The Multiple Comparison Procedure – Modelling (MCP-Mod) approach is a hybrid approach that combines hypothesis testing and modelling, offers a modelling-based quantitative approach to dose selection. It overcomes the shortcomings of traditional dose selection methods and provides the flexibility of modelling for dose estimation, while preserving the robustness to model misspecification associated with MCP. This approach has been qualified by regulatory agencies (e.g., EMA in 2014[16] and FDA in 2016[17]) as an efficient statistical method for Phase II dose-finding studies when there is uncertainty about dose-response relationship.

9.3 PROPOSED STATISTICAL ANALYSIS PLAN (BASED ON COMBINED UK AND ITALIAN RECRUITMENT)

We will recruit 30 participants into this study, who will be randomised into one of three doses (25, 50 and 75mg once daily). The study primary outcome will be reduction in CTX over the 24 week period of the study. The Multiple Comparison Procedure – Modelling (MCP-Mod) method will be used for finding the optimal dose.[18]

A set of prespecified candidate models will be used to assess the presence of a dose response signal (MCP-step). Then the optimal dose will be selected based on the parametric modelling (Mod step). We will repeat this analysis at 24-week follow-up, in order to assess the maximum reduction in CTX at long term follow-up. The analysis will be undertaken by DoseFinding package in R version 4.1.

In terms of study safety/tolerability outcomes, we will summarise each safety event during the 24-week follow-up period by dose group. Additionally, we will report the number/percentage of patients who cannot achieve the allocated dose (particular for the 50 and 75 mg dose). For safety monitoring purpose, we will periodically report to Data Monitoring and Ethics Committee (DMEC) at pre-specified timepoints about patient dose calculation algorithm and reasons for no escalation decision (potassium and hypotension).

9.4 OUTCOMES

Primary outcomes measures: percentage change in CTX reduction over the 24 week period of the study.

Secondary outcome measures:

- Percentage change in CTX at 8 week
- Percentage change in TGFβ & P1NP at week 8
- Percentage change in TGFβ & P1NP over the 24 week period of the study
- changes in proxy efficacy outcomes of bone (mass, architecture and strength) using High Resolution peripheral Quantitative CT (HRpQCT), Dual Energy X-ray Absorptiometry (DXA)
    - Change in DXA LSaBMD
    - Change in radial and tibial total vBMD by HRpQCT
- changes in proxy efficacy outcomes of muscle (strength) using the “Timed Up and Go” test
- Change in OI QoL, a validated disease-specific tool

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• To establish the effective dose of losartan in 30 older adolescents and adults aged 16 years and above with OI, based on maximal reduction in the bone resorption marker carboxy-terminal crosslink of type I collagen telopeptide (CTX)	• Percentage change in CTX over the 24 week period of the study
• To determine the changes in proxy efficacy outcomes for bone (turn over, mass, architecture and strength) using blood test, High Resolution peripheral Quantitative CT (HRpQCT), Dual Energy X-ray Absorptiometry (DXA) and muscle (strength) using the "Timed Up and Go" test • To determine changes in quality of life using a validated disease-specific tool (OI-QoL)	• Percentage change in CTX at 8 week • Percentage change in TGFβ & P1NP at week 8 • Percentage change in in TGFβ & P1NP over the 24 week period of the study • Change in DXA LSaBMD • Change in radial and tibial total vBMD by HRpQCT • Change in Timed Up and Go test • Change in OI QoL

9.5 MISSING DATA

Missing data will be assessed for any differential 'missingness' between randomised groups and investigated using appropriate missing data mechanisms. Details will be provided in the Statistical Analysis Plan.

9.6 INTERIM ANALYSIS AND CRITERIA FOR PREMATURE TERMINATION OF THE STUDY

The DMEC will meet at three-monthly intervals in order to ensure that there is no emergent safety signal for any specific dose. If treatment with 25mg losartan is not tolerated by the majority of the participants, then a Trial Steering Committee (TSC) meeting will be convened together with the site PIs to discuss whether to continue with the study.

10.0 DATA COLLECTION

A study specific Data Management Plan agreed by the Chief Investigator, Sponsor, HHTU statistician will be drafted to provide detailed instructions and guidance relevant to database set up, data entry, validation, review, query generation and resolution, quality control processes involving data access and transfer of data to the sponsor at the end of the study and archiving.

Data management for Italian sites will follow UK Data Management Plans and study database development processes. CRFs will be translated into Italian to ensure consistency of data collection across all sites. Italian sites will enter study data into the same study database as English sites to facilitate data analysis and monitoring during the study.

A statement of permission to access source data by study staff and for regulatory and audit purposes will be included within the participant consent form with explicit explanation as part of the consent process and Participant Information Sheet. In principle, anonymised data will be made available for meta-analysis and where requested by other authorised researchers and journals for publication purposes. Requests for access to data will be reviewed by the Chief Investigator and Study Sponsor.

The Investigator(s)/Institution will permit monitoring, audits, REC and MHRA review (as applicable) and provide direct access to source data and documents.

10.1 DATA COLLECTION AND SOURCE DOCUMENT IDENTIFICATION

10.1.1 RECORD OF STUDY CONTACT IN CLINICAL NOTES

As a minimum, the following information will be recorded in participants' medical notes for study visits or

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telephone contacts:

- Clearly written date of visit or contact, brief study title/acronym and visit number
- Date patient given Patient Information Sheet and which version was given
- Date and version of Consent Form signed
- Date of screening
- Medical history, co-morbidities and medication, and any changes in co-morbidities and concomitant medication at subsequent visits
- Anything which is relevant to the ongoing care of the patient:
    - Relevant results and study doctor's assessment of these results
    - Brief description of any AEs with start and stop times/dates and any significant test results or a medical summary of events if more appropriate
- Any other relevant information

10.1.2 SOURCE DATA

In this study, data will be sourced from the following as seen in Table 2:
Please refer to Table 1: study interventions Schedule detailed on Page 28, regarding timing and types of assessment.

TABLE 2: STUDY SOURCE DATA TABLE

Assessment	Data Source	Completed by
Eligibility	Medical notes	Study Doctor
Consent	Medical notes and study consent form	Study Doctor
Demography, BMI [Height, Weight], Vital signs: BP, P, Temperature, Respiratory rate, O_2 Saturations	Medical notes, Case Report Form	Study Nurse, Study Doctor
Past Medical History, clinical examination, Fracture history, Pubertal stage assessment	Medical notes,	Study Doctor
Urine pregnancy test (WOCBP)	Medical notes, Case Report Form	Study Nurse, Study Doctor
Questionnaire: OI Quality of Life	Participant questionnaire	Participant
Randomisation assignation	REDCap Cloud database, medical records	Study Nurse, Study Doctor
Dose escalation / Dose modification decision [Serum K+, Symptoms of hypotension assessment]	Medical Records, Case Report Form, pathology reports in medical notes	Study Doctor, pathology service
Scan results HRpQCT Scan radius and tibia DXA LS and Hip	Radiology Report in medical notes	Study Doctor
Timed "up and go" test	Medical Notes, Case Report Form	Study Nurse, Study Doctor
Fracture incidence	Medical Notes, Case Report Form	Study Doctor
Blood tests [FBC, U&Es, LFTs] Fasting blood tests [CTX, losartan TGFβ, P1NP Bone profile 25OHD, PTH];	Pathology Reports in medical notes	Pathology service
Urine dipstick	Medical Notes, Case Report Form	Study Nurse, Study Doctor

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Drug Accountability	Participant diary, prescriptions, pharmacy records	Participant, Pharmacist, Study Nnurse
Adverse Event assessments	Medical notes, Case Report Form	Study Doctor

10.1.3 CASE REPORT FORMS

Individual participant data required by the study protocol will be recorded on the study case report form (CRF). Site research staff will enter collected data from the paper CRF onto the electronic study database provided by the HHTU. The design of the CRF will:

- enable adequate collection of data
- provide an audit trail to demonstrate the validity of the study (both during and after the study)
- ensure that only the data required by the protocol are captured

The participating sites will retain a copy of the paper CRFs and a copy of the data entered on the study database to ensure that the PI can provide access to the source documents to a monitor, auditor, or regulatory agency to check for any transcription errors.

10.2 MINIMISATION OF MISSING DATA

Efforts to minimise missing data will be made as follows:

- Use of minimal and short-form questionnaires
- Maintaining regular contact with participants
- Minimum requirement for participant to attend hospital for study assessments
- Provision of accommodation and travel support for overnight stays at baseline and week 24
- The reasons for missing data and study withdrawal will be actively monitored throughout the study, in keeping with International Council for Harmonisation Good Clinical Practice (ICH GCP).

10.3 DATA HANDLING AND RECORD KEEPING

Full details are given in the study specific Data Management Plan.
Study data will be recorded for both study administration and collection of participant data.
All data will be completely anonymised for purposes of analysis and any subsequent reports or publications. For the purposes of ongoing data management, once created as a Subject on the REDCap (RCC) database, individual participants will only be identified by their unique Subject ID Number. Paper Case Report Forms (CRFs) will be created by HHTU as part of the RCC database build, test and release process.

10.3.1 DATA ENTRY

The data collected by sites using paper questionnaires will be entered by the site into the RCC specifically developed for this study. Confirmation of the data received by HHTU will be given to the site. If a site used a paper CRF, the data will be entered into RCC and the paper CRF will remain at the recruiting site as source data. Data will be checked according to procedures detailed in the study specific Data Management Plan.

10.3.2 DATA STORAGE

Each site will hold data according to the General Data Protection Regulation Act (2018) and data will be collated in CRFs identified by a unique Subject ID Number. Once enrolled as a Subject on RCC, the automatically RCC generated Subject ID Number unique to each participant will be used on all subsequent forms and documents.

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For example, the Subject ID Number will contain a number to identify the site and a sequential number unique to each participant. Sites will have the prefix of MOI. Each site will be allocated a site number during study set up. If the first participant recruited to the study is from site 02, the Subject ID Number will be MOI-02-01. If the second participant is recruited from site 04, the Subject ID Number will be MOI-04-02.
All study documents will be stored in accordance with GCP guidelines and GDPR 2018 regulations. RCC database access will be controlled by HHTU Data Management team.

Study documents (paper and electronic) will be retained in a secure (locked when not in use) location during and after the study has finished. All essential documents, including source documents, will be retained for a minimum period of 25 years after study completion. Where the site NHS Trust procedures allow, a sticker stating the date after which the documents can be destroyed will be placed on the inside front cover of the case notes of study participants.

HHTU (based within University of Hull) have backup procedures approved by auditors for disaster recovery. There will be a separate archival of electronic data performed at the end of the study to safeguard the data in accordance with regulatory requirements.

RCC EDC data will be analysed by the HHTU Statistician at the end of the study reporting. Sites will receive a copy of their locked dataset before the final analysis takes place. RCC EDC data transfer will comply with the General Data Protection Regulation Act (2018). Further details regarding data storage and transfer will be given in the study Data Management Plan.

10.4 ACCESS TO DATA

Direct access will be granted to authorised representatives from the sponsor, host institution and the regulatory authorities to permit study-related monitoring, audits and inspections.
HHTU Data Management Team will control access permissions to the RCC database and the electronic Trial Master File (eTMF) throughout the study and afterwards when the documents have been archived. Access permission will be granted based on delegated study role and level of access required e.g. editor or read only. Access will be revoked when staff leave the study or at the end of the study after Data Lock.

10.5 ACCESS TO THE FINAL TRIAL DATASET

The database will be 'locked' to obtain the final dataset after:

- study data collection completion (Last Participant, Last Visit)
- completion of coding and data entry
- all data queries resolved and the database updated, any serious adverse event queries have been resolved and the database updated
- study team notified of date of lock

A copy of the final study dataset and end of study notification will be sent to the sponsor before the randomisation list will be released by HHTU prior to the statistical analysis. A copy of individual site's data will be sent to that site.

A copy of the final study dataset will be archived by the HHTU and sent to the Chief Investigator(s). Other authorised, researchers requesting access to the dataset for further research may apply through the Chief Investigator(s). Applications will be considered in keeping with the publications policy which will be agreed by the Trial Steering Committee.

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10.6 SITE FILE MANAGEMENT

The study will use an electronic Trial Master File (eTMF) and paper Investigator Site Files (pISF).
The eTMF will be held on BOX managed by the HHTU Data Management Team. Access will be restricted to those who delegated on the HHTU or site delegation logs and will be granted based on role and level of access required.
HHTU will organise the Investigator site files for the UK sites and Italy will organise theirs.

10.7 ARCHIVING

Archiving will be authorised by the sponsor following submission of the end of study report. All essential study documents including source documents will be archived in accordance with the HHTU Trial Data Management. Plan for a minimum period of 25 years after study completion. Destruction of essential documents will require authorisation from the sponsor.
Where permitted in site NHS Trusts, a sticker stating the date after which the documents can be destroyed will be placed on the inside front cover of paper medical records of study participants.

11.0 PHARMACOVIGILANCE / SAFETY PROCEDURES

11.1 DEFINITIONS OF SAFETY REPORTING

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication 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 trial medication qualify as adverse reactions.

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Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. 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.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out: • in the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product

NOTE: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above and relates to the consequence of the event.

Monitoring and reporting of pharmacovigilance aspects of the study will be in accordance with the study SOPs and detailed in the Study Monitoring Plan.

11.2 AE RECORDING AND ASSESSMENT

All AEs will be reported to HHTU via the RCC database as soon as possible after site teams become aware of the event. Sites will be responsible for collecting AE data and entering data into the RCC database. The PI or delegated study doctor will be responsible for assessing AEs in relation to seriousness and causality. The AE reporting period begins as soon as a participant is consented to the study and will continue for 30 days after the last study visit. If an AE is assessed by the PI as serious, SAE events will be reported to HHTU within 24 hours of site teams becoming aware of the event. See Section 11.4.

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11.3 SERIOUS ADVERSE EVENTS / SERIOUS ADVERSE REACTIONS

Participants are not expected to have a high morbidity or mortality during the study period due to the eligibility criteria requiring participants to have either stable disease or be well enough to tolerate losartan treatment. In addition, the study is administering an IMP that has Marketing Authorisation. However, as this is a feasibility study involving dose escalation methodology, all SAE events will be reported. There are no SAE exemptions in this study. SAEs reporting will being as soon as consent is taken, whereas SAR / SUSAR reporting will not start until they have had their first study IMP administration. There are no expected SARs for this study population other than those listed in section 4.8 of the SmPC for losartan potassium.

Where a participant withdraws consent for further processing of data, this does not include the reporting of SARs and SUSARs which are still required to be reported for regulatory purposes. SAEs/ SARs will be evaluated for duration and intensity by the PI / delegated study doctor using the National Cancer Institute of Common Terminology for Adverse Events (NCI-CTCAE) Version 5.0. The CI and sponsor will assess SAE / SAR expectedness according to the approved version of the Reference Safety Information (RSI) which in this case will be the Summary of Product Characteristics (SmPC). The CI will consult with the clinical co-investigator whist assessing the expectedness and causality. If either the PI, CIs or sponsor suspect a causal relationship with an unlisted, unexpected reaction is 'highly probable', 'probable', or 'possible', this will be reported as a SUSAR, as will all individually reported SARs. In case of ARs assessed as 'unknown' or 'not assessed' for which the investigator cannot make a decision with regard to relatedness to the IMP, in accordance with CT-3 European Commission guidelines, the sponsor will consult the reporting investigator and encourage him/her to express an opinion. Robust justification will be provided in each instance of SUSAR reporting. No life-threatening or fatal SARs are expected with losartan.

If the SmPC is updated during the study, the CI and sponsor will consider whether the risk: benefit ratio has changed and whether any study protocol mitigations are warranted. If there is a change, an updated SmPC will be sent to the MHRA along with any other study document changes via a substantial amendment.

11.4 SAFETY REPORTING PROCESS

The pharmacovigilance SOP and study specific instructions about the process for reporting must be followed. Sites will receive training on pharmacovigilance reporting during site set-up, and copies of SOPs/Instructions will be available in the study site file. All SAEs will be reported to the sponsor by HHTU within 24 hours.
HHTU will responsible for processing safety reports for this study and will follow the relevant HHTU SOPs.

The study site will report all SAEs to HHTU within 24 hours of becoming aware of an event. HHTU will inform the CI and sponsor as soon as they become aware of the event and within 24 hours of the notification. If the SAE initial report does not include a causality assessment, HHTU will request a follow-up SAE report as soon as possible until causality and a final outcome is determined. The CI and sponsor will determine SAE expectedness within 24 hours of receiving the SAE form from HHTU using the approved version of the study Reference Safety Information (RSI), which in this study will be the SmPC. SUSARs must be reported to the Sponsor within 24 hours of the study team becoming aware of them.

The Sponsor will then work with you to coordinate onward reporting, within the following timelines:

- For CTIMPs & CIMDs, fatal or life-threatening SUSARs must be reported to the REC and MHRA within 7 days.
- All other SUSARs must be reported within 15 days.
- Events will be followed up until resolved or a final outcome has been reached.

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Each SAE will be identified by the participant number and SAE number e.g. MOI-01-02-SAE-001, and will be documented on a SAE log kept in the pISF. SAE events will be reported directly via the study database, although there will be a corresponding paper form in the event that RCC is not available, which will be scanned and emailed to HHTU (**hhtusafetyreporting@hyms.ac.uk**).

In the study database, there will be an 'initial' SAE report form and a 'follow up' SAE form. The 'initial' SAE form will capture the early data about the event but may not be able to report a SAE outcome. The 'follow up' SAE form will be used to provide ongoing updates about the event. Several 'follow up' SAE forms may be required until an outcome is determined by the site PI. The Paper Initial SAE form, only to be used if the study database is unavailable, will be entered as soon as it becomes available. There will be no paper Follow Up SAE reports as these will be entered into the study database directly.
When the SAE event is entered into the study database, an automatic alert will notify the HHTU team when a SAE form has been created. Assessment of severity, seriousness and causality will be made by the PI or authorised Study Doctor on the delegation log. The CI in consultation with the clinical Co-Investigator(s) will decide whether the serious event is an SAE or SAR by assessing whether the event is either unrelated or possibly related to the IMP (causality).

If the event is possibly related then it is a SAR and an assessment needs to be made by the CI, on behalf of the sponsor, as to whether the event is expected or not for the IMP. If the SAR is listed in the MHRA approved SmPC (RSI) then it is expected. The CI will assess causality and document the assessment on the SAE form but this must be done after the PI. PI assessment of causality must not be downgraded by the CI. If the site PI/Clinical co-investigator is unavailable, initial reports without a causality and seriousness assessment will still be submitted to HHTU within 24 hours of becoming aware of the SAE, but will be followed-up by a medical assessment as soon as possible. The PI/Study Doctor must always review the SAE form and sign to confirm the contents of the report are accurate and complete. Any change in participant condition or additional relevant follow-up information will be reported to the sponsor as soon as it becomes available. The PI will assess causality again on the follow-up SAE form and if the PIs opinion on causality changes, the CI will need to reassess causality.

If the SAE changes to a SAR, then the CI will assess expectedness. SAE/SARs will be followed up until resolved or a final outcome has been reached. All SAEs / SARs assigned by the PI/Study Doctor as possibly related to IMP treatment and those the CI has assessed as unexpected will be classified as SUSARs and will be subject to expedited reporting to the MHRA. The Sponsor will inform the MHRA and the REC of SUSARs within the required expedited reporting timescales.

The progress of the study, safety issues and reports, including expedited reporting of SUSARs, will be reported to the relevant Clinical Trial Authorisation (CTA) in accordance with relevant national and local requirements and practices.

11.5 END OF STUDY

The end of the study will be defined as completion of sample analysis.. An End of Study Declaration Form will be submitted to the REC, Health Research Authority (HRA) and MHRA and site R&D within 90 days from the End of Study date and within 15 days if the study is discontinued prematurely. A summary of the study final report/publication will be submitted to the, REC, HRA and MHRA and site R&D within 1 year of the end of study date. Site R&D will be notified immediately of any reason to halt the study. The CI and sponsor will decide if the study should be halted temporarily. The REC and site R&D will be notified within 15 days of a decision to temporarily halt the study by submitting a substantial amendment notification.

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12.0 RESEARCH GOVERNANCE AND QUALITY CONTROL

In the UK the study will be performed subject to Research Ethics Committee favourable opinion, MHRA Clinical Trial Authorisation, sponsor and NHS Trust site permissions. The study will be conducted in accordance with The Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments; the International Conference for Harmonisation of Good Clinical Practice (ICH GCP) guidelines; and the UK Policy Framework for Health and Social Care Research.
In Italy, the study team will request corresponding regulatory approvals from their relevant authorities.

12.1 STUDY ORGANISATION STRUCTURES AND RESPONSIBILITIES

The UK study sponsor will be Sheffield Children Hospitals NHS Foundation Trust (SCH) who will have overall responsibility for the conduct of the study in the UK . The study will be managed by the HHTU, on behalf of Professor Nicholas Bishop (Chief Investigator). The UK sites in this study will be monitored by HHTU in accordance with HHTU's Standard Operating Procedures to ensure compliance with UK Clinical Trial Regulations. All study related documents will be made available upon request for monitoring by HHTU monitors and for inspection by the MHRA.

12.1.1 CHIEF INVESTIGATOR (CI)

The CI will overall responsibility for study design, coordination and management, including but not limited to:

- Study authorisation including responsibility for the protocol, and obtaining approvals from the MHRA, REC and R&D
- Ensuring that the study is conducted according to the UK Clinical Trial regulations and GCP
- Assessment of SAEs and expedited reporting of any SUSARs to the MHRA

12.1.2 HULL HEALTH TRIALS UNIT (HHTU)

The sponsor, Chief Investigator, HHTU (Trial Management, Data Management and Statistics) will be stipulated clearly in the sponsor-collaboration agreement

12.1.3 STATISTICAL ANALYSIS

Dr Chao Huang employed by University of Hull, will oversee the statistical aspects of the study including the drafting of the Statistical Analysis Plan, the conduct of analyses and reporting of results.

12.1.4 THE PRINCIPAL INVESTIGATOR (PI)

The PI at each participating site will be responsible for local site-specific assessment approval and for the local conduct of the study. All correspondence relating to the study at site should be filed in the pISF and maintained by the site study team.

12.1.5 SITE STUDY TEAMS

Authorised study doctors are permitted to take consent, confirm eligibility, prescribe the study IMP and make dose escalation/modification decisions. Study nurses are responsible for the management of patient recruitment, support for the consent process and co-ordination of all aspects of data collection. Sites are responsible for conducting the study in accordance with the protocol, SOPs, contract agreements, the UK Clinical Trial Regulations and GCP.

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12.2 TRIAL MANAGEMENT, MONITORING AND OVERSIGHT

12.2.1 INDEPENDENT DATA MONITORING AND ETHICS COMMITTEE (DMEC)

The DMEC will review the safety and ethics of the study by reviewing interim data approximately every 3 months from the start of recruitment and membership to this group will include an independent statistician. The Terms of Reference of the DMEC are to:

- Ensure that patient considerations are of prime importance
- To review any safety issues arising during the study (including any SAEs, SARs and SUSARs)
- To report (following each DMEC meeting) its recommendations regarding study continuation to the Trial Steering Committee
- To consider any requests for release of interim study data and to make recommendations to the Trial Steering Committee on the advisability of this
- Should data summaries be required during the study, to provide to the Trial Steering Committee appropriate information and advice on the data gathered to date that will not jeopardise the integrity of the study
- The DMEC will not consider matters in relation to the implementation study aspects of the study

The DMEC will consist of:

- An experienced OI physician
- An experienced physician with relevant experience
- A clinical trials statistician

12.2.2 TRIAL STEERING COMMITTEE (TSC)

The TSC will provide overall supervision of the study, in particular study progress, adherence to protocol, patient safety and consideration of new information. An independent chair will be appointed, two other independent members and at least two PPI attendees. The Committee will meet approximately every 3 months. The Terms of Reference of the Trial Steering Committee are as follows:

- To provide overall supervision of the study, ensuring adherence to protocol
- To review developments during the study and recommend appropriate action
- To ensure that the rights, safety and well-being of study participants is safeguarded and prioritised
- To review at regular intervals relevant information from other sources (e.g. other related studies), and recommend appropriate action (e.g. changes to study protocol, stopping or extending the study)
- To keep any issues discussed in the meetings or written in the minutes confidential, unless otherwise agreed
- The TSC will also consider matters pertaining to the implementation study aspects of the study

12.2.3 TRIAL MANAGEMENT GROUP (TMG)

The TMG will comprise of the Chief Investigator, other lead investigators (clinical and non-clinical), members with a specific interest (e.g. nurses; patient representatives), and members of HHTU and a sponsor representative. The TMG will also consider matters pertaining to the implementation study aspects of the study.

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12.3 QUALITY CONTROL

12.3.1 TRAINING

The following training procedures will be conducted to ensure quality control.

Person trained	Description
Study nurse, Site Principal Investigator/nominated clinicians	• Blood sample collection and storage • Data collection and management • Safety and efficacy assessments • Randomisation • "Timed up and go" test
Site Principal Investigator / nominated clinicians	• Eligibility assessment • Consent procedure (and ICH GCP if consenting patients) • Prescription – Dose modification decision • HRpQCT scan radius and tibia • DXA LS and Hip
Clinical trials pharmacist	• Labelling • Medication preparation • Dispensing procedures

12.3.2 BLOOD SAMPLING

Venous blood samples will be drawn a various timepoints during the study. Study nurse competency in blood sampling will be recorded at the study site, with a copy filed in each Investigator site file, if available. Routine blood sample pathology results will be filed in the participants' s medical notes as source data. Each study site must print off the appropriate results, with the date of printing, have the results reviewed by the PI/Study Doctor, and have the results signed and dated. The site will keep a copy of the pathology service guidelines for obtaining, transporting and storing blood samples. Blood samples will be destroyed after analysis.

12.4 SITE APPROVAL, START-UP PROCEDURES AND ONGOING SUPPORT

The following documentation must be received by HHTU in order for a site to start recruitment to the study. This list is not exhaustive and will follow the Sponsor's Working Instruction:

- A copy of HRA approval and site R&D Capability and Capacity assessment
- A copy of signed Clinical Trial Agreement including Principal Investigator agreement
- Completed Investigator Statement, signed by the institution Principal Investigator on behalf of all staff at the site who will be working on the study
- Completed Delegation Log and Contact Details
- ISF Checklist signed by a member of the research team
- CVs, including evidence of GCP training for named persons
- Copies of honorary contracts
- Pharmacy technical release Greenlight

Once these documents have been received by HHTU, confirmation that the site may commence recruitment will be sent to the site PI by the sponsor (Site Greenlight).

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Prior to recruitment, each study site team including the PI will attend a Site Initiation Visit (SIV), either face-to-face or via tele/video conference by HHTU. Clinicians and research teams (including pharmacy) at site will be trained in the data collection, data entry, filing and study interventions in order to comply with GCP. At the SIV study and pharmacy procedures will be clarified, the protocol reviewed in detail and a pharmacy and laboratory manual provided. A Site Initiation Report will be written and a copy sent to the study site.
Remote and onsite will be provided to sites as per their requirements during the course of the study, mainly by the HHTU Trial Coordinators, with the support of HHTU Trial Managers as appropriate.

12.5 MONITORING, AUDIT AND INSPECTION

The study will be monitored in accordance with HHTU Standard Operating Procedures and Study Monitoring Plan to ensure compliance with UK Clinical Trial Regulations and ICH GCP. All study related documents will be made available upon request for monitoring by HHTU monitors and for inspection by the MHRA.
Full details are given in the Study Monitoring Plan which will be developed and agreed by the sponsor, CI, TMG and TSC based on the study risk assessment. Monitoring will be a combination of central, on- site and remote monitoring, with appropriate risk adaptations considered during the risk assessment. HHTU will co-ordinate and perform monitoring and submit reports to the sites and sponsor, and escalate findings as required.
HHTU will be responsible for undertaking monitoring activities for this study at UK sites. Italian study managers will undertake monitoring activities in Italian sites.

13.0 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 ETHICAL CONSIDERATIONS

This is a Clinical Trial of an Investigational Medicinal Product (IMP) as defined by the EU Directive 2001/20/EC. A Clinical Trial Authorisation (CTA) is required in each EU participating country. This study will recruit in the UK and Italy and each will submit their study protocol to their own National Competent Authorities. This study protocol will be submitted to the MHRA in the UK.

As part of study set up and before initiation of the study at any clinical site, the protocol, informed consent forms and any material to be given to the prospective participant will be submitted to the relevant national REC and national research authority (e.g. MHRA, HRA in the UK) for approval. Any subsequent amendments to these documents will be submitted for further approval. Each site will provide R&D Capacity and Capability (C&C) approval before the study can be given the greenlight to start recruitment.

13.2 RESEARCH ETHICS COMMITTEE (REC) REVIEW AND REPORTS

The following will be observed:
• Before the start of the study, approval will be sought from REC for the study protocol, informed consent forms and other relevant study documents e.g. GP information letters
• Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the study (note that amendments may also need to be reviewed and accepted by the MHRA and/or NHS R&D departments before they can be implemented in practice at sites)
• All correspondence with the REC will be retained in the Trial Master File/Investigator Site File
• An Annual Progress Report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the study is declared ended
• The Chief Investigator will be responsible for the annual and end of study reports as required

13.3. REGULATORY COMPLIANCE

The study will comply with the following regulations:

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• *The study will be submitted to and approved by a National REC prior to entering participants into the study*
• *The study will not commence until a Clinical Trial Authorisation (CTA) is obtained from the MHRA*
• *The protocol and study conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments*
• Before site can enrol participants into the study, the Chief Investigator/Principal Investigator or designee will apply for NHS HRA permission and complete a Capacity and Capability (C&C) assessment with the site R&D department

13.4. AMENDMENTS

If the Sponsor wishes to make a substantial amendment, all amendments will be submitted via the Combined IRAS Gateway The MHRA and/or the REC will provide a response regarding the amendment within 35 days of receipt of the notice. It is the Sponsor's responsibility to decide whether an amendment is substantial or non-substantial for the purposes of submission to the MHRA and/or REC. The process for making and communicating amendments will be as described in the relevant HHTU Standard Operating Procedure. Under the Medicines for Human Use (Clinical Trials) Regulations 2004, the sponsor may make a non-substantial amendment at any time during a study. There is no requirement for investigators to notify the MHRA of non-substantial amendments, however the REC and HRA must be notified.

Participating site R&D teams need to be notified of amendments to assess whether it affects NHS capability and capacity for that site.

13.5 PROTOCOL COMPLIANCE

Protocol deviations, violations, or breaches are defined as departures from the approved protocol.
• Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and will not be used e.g. patients will not be enrolled if they do not meet the eligibility criteria or restrictions specified in the study protocol.
• Accidental protocol deviations can happen at any time. They will be adequately documented on the relevant forms and reported to the Chief Investigator and sponsor immediately.
• Deviations from the protocol which are found to frequently recur will require immediate action and may be classified as a serious breach.

13.6 NOTIFICATION OF SERIOUS BREACHES TO GCP AND/OR THE PROTOCOL

A "serious breach" is a breach which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the participants of the study

or

(b) the scientific value of the study in the event of a serious breach

• The sponsor will be notified immediately of any case where the above definition applies during the study conduct phase
• The sponsor will notify the MHRA in writing of any serious breach of (a) the conditions and principles of GCP in connection with that study; or (b) the protocol relating to that study, as amended from time to time, within 7 days of becoming aware of that breach

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13.7 CONFLICTS OF INTEREST

Any competing interests that might influence study design, conduct, or reporting will be identified, disclosed and documented in the eTMF. Oversight groups will determine what it is appropriate to report; details will be in the Dissemination and Publication Plan. Disclosure should reflect:

- ownership interests that may be related to products, services, or interventions considered for use in the study or that may be significantly affected by the study
- commercial ties requiring disclosure include, but are not restricted to, any pharmaceutical, behaviour modification, and/or technology company
- any non-commercial potential conflicts e.g. professional collaborations that may impact on academic promotion

13.8 DATA PROTECTION AND PATIENT CONFIDENTIALITY

Full details will be available in the Study Data Management Plan, Data Protection Impact Assessment (DPIA) and Privacy Notice. The HHTU data management team will be responsible for insuring compliance with General Data Protection Regulation 2018.

All site investigators and research staff must comply with the requirements of the General Data Protection Regulation 2018 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Regulation's core principles.

HHTU and sponsor will maintain the confidentiality of all participant data in accordance with General Data Protection Regulation Act (2018) and will not reproduce or disclose any information by which participants could be identified. Representatives of HHTU and sponsor will need access to patients' medical records for the purposes of monitoring and source data verification. Confidentiality will be maintained at all times. Representatives of regulatory authorities may require access to participant medical records for regulatory purposes only. These points will be made clear in the Patient Information Sheet and Informed Consent Form.

The patient's full name, date of birth, hospital number and NHS number or equivalent, will be collected to enable tracing through national records. The site PI (or delegated person) at each site will keep a participant register of Subject ID Number, names, addresses and hospital and NHS numbers. The PI must ensure that confidentiality is maintained and that all study documents (e.g. consent forms) are maintained in strict confidence.

13.9 FINANCIAL AND OTHER COMPETING INTERESTS FOR THE CHIEF INVESTIGATOR, PIS AT EACH SITE AND COMMITTEE MEMBERS FOR THE OVERALL TRIAL MANAGEMENT

Any competing interests that might influence study design, conduct, or reporting will be identified, disclosed and documented in the eTMF. The oversight groups will determine what it is appropriate to report; details will be in the Dissemination and Publication Plan.

Disclosure should reflect:

- ownership interests that may be related to products, services, or interventions considered for use in the study or that may be significantly affected by the study
- commercial ties requiring disclosure include, but are not restricted to, any pharmaceutical, behaviour modification, and/or technology company
- any non-commercial potential conflicts e.g. professional collaborations that may impact on academic promotion

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13.10 GENERAL ETHICAL CONSIDERATIONS

The patient population under study is a group living with significant disease and care should be taken not to introduce further physical, psychological or financial burden with entry into studies. However, this must be balanced with the need to test practices. In order to try to address some of these concerns, this study:

- Includes a research team with a broad base of clinical experience including OI care
- Minimises the need for hospital visits, by employing sufficient study nurses to allow home visits
- Uses assessments kept to short form and non-invasive techniques
- Will reimburse reasonable travel costs, accommodation and refreshment
- Provides support for participants as part of study nurse role

14.0 INDEMNITY

14.1 POTENTIAL LEGAL LIABILITY OF THE SPONSOR OR EMPLOYER

This is an NHS sponsored study and NHS indemnity covers sponsor potential legal liability for harm to UK participants arising from the design of the research. Protocol authors with a substantive UK university contract will also have indemnity cover from their employing university. Italy will follow their national indemnity policies.

14.2 POTENTIAL LEGAL LIABILITY OF INVESTIGATORS/COLLABORATORS

If there is negligent harm during the clinical trial, the NHS body owes a duty of care to the person harmed. NHS indemnity covers NHS staff and UK based medical academic staff with honorary contracts only when the study has received confirmation of capability and capacity from the Trust R&D department.

14.3 ARRANGEMENTS IN THE ABSENCE OF LEGAL LIABILITY

NHS indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Protocol authors with a substantive UK university contract will also have indemnity cover from their employing university. The UK universities do not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm.

The sponsor will not provide 'no-fault' indemnity for harm arising due to study procedures carried out as part of the study. The sponsor will not provide payment for medical costs for medical complications caused by failure of participants to follow instructions given or if the medical complication was not related to the study agent or research study procedure. Study associated staff employed by NHS and UK university will also have personal indemnity from their employers.

15.0 PUBLIC AND PATIENT INVOLVEMENT

The study OI PPI Group informed this study and support the value to patients of quantifying the net effects (benefits and side-effects) of losartan in OI. The PPI group felt that the intervention and assessments were acceptable.

Patients will be involved in all aspects of study monitoring. PPI members will also provide advice as Trial Steering Committee members. They will be mentored and trained by the PPI facilitator, and supported by the OI PPI group. A study team PPI lead will coordinate and facilitate this activity. PPI group members will be on the Trial Management Group, mentored by a member of the HHTU team. We are committed to active patient involvement at all stages of the study to ensure the research is grounded and relevant to the experiences of patients, family members and the wider public. As members of the Trial Management Committee, patients

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will be involved in all practical and strategic decisions about study conduct and management. Lay members will also be involved in the interpretation of analysed findings, and dissemination.

16.0 PUBLICATION POLICY

16.1 DISSEMINATION POLICY

Publications for the study will meet the standards required for submission to high quality peer reviewed journals and will be reported in accordance with the CONSORT guidance. **http://www.consort-statement.org/.**

On completion of the study, the data will be analysed and tabulated and a Final Study Report prepared.

The results will be disseminated in peer reviewed journals, through local OI, orthopaedic and other relevant clinical networks and at national and international meetings. Patients participating in the study will be sent a summary of the findings, if requested, coordinated at site level. Participants may request the summary results from their PI after the Final Study Report, and a copy of the final accepted manuscript of the primary paper after the results have been published.
The funding source will be acknowledged within all publications, and a copy sent for their prior information according to their requirements. The Funder does not have publication rights of the data from the study.

The study protocol manuscript will be prepared and published. The protocol will be available on the CI and HHTU website, and the study design synopsis available on the ISRCTN and EudraCT website. The participant level dataset will be available to authorised researchers through application to the CI.
Professional medical writers will not be hired.

16.2 AUTHORSHIP ELIGIBILITY GUIDELINES AND ANY INTENDED USE OF PROFESSIONAL WRITERS

All publications and presentations relating to the study are required to be authorised by the Study Steering Group (SSG), who will prepare the Study Dissemination and Publications Plan.
The agreement will include:

- guidelines on authorship on the final trial report consistent with the Vancouver Recommendations from The International Committee of Medical Journal Editors
- whether participating investigators have rights to publish any of the study data
- any time limits or review requirements on the publications

Professional medical writers will not be hired.

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