Study Protocol

Treatment of Osteogenesis Imperfecta with Parathyroid hormone and Zoledronic acid

the TOPaZ trial

TOPaZ

Co-sponsors	University of Edinburgh & NHS Lothian ACCORD The Queen's Medical Research Institute 47 Little France Crescent Edinburgh EH16 4TJ
Funder	This project is funded by the Efficacy and Mechanism Evaluation (EME) Programme, an (Medical Research Council) MRC and National Institute for Health Research (NIHR) partnership Eli Lilly (supply of teriparatide only)
Funding Reference Number	EME 14/200/18
Chief Investigator	Professor Stuart Ralston
EudraCT Number	2016-003228-22
REC Number	16/ES/0110
Protocol Number	AC16092
ISRCTN Number	ISRCTN 15313991
Version Number and Date	Version 8.0 07Feb2019

COORDINATING CENTRE

Chief Investigator	**Co-sponsor Representative**
Professor Stuart Ralston Molecular Medicine Centre Institute of Genetics & Molecular Medicine Western General Hospital Edinburgh EH4 2XU	Fiach O'Mahony The Queen's Medical Research Institute 47 Little France Crescent Edinburgh EH16 4TJ

Tel: 0131 651 8743 Fax: 0131 651 1085 Email: stuart.ralston@ed.ac.uk	Tel: 0131 242 9418 Fax: 0131 242 9447 Email: resgov@accord.scot
Trial Manager Holly Ennis Edinburgh Clinical Trials Unit The University of Edinburgh Edinburgh Bioquarter 9 Little France Road Edinburgh EH16 4UX Tel: 0131 651 9915 Email: holly.ennis@ed.ac.uk	**Trial Statistician** **Trial Statistician** Professor Christopher Weir Centre for Population Health Sciences The University of Edinburgh Medical School, Teviot Place Edinburgh EH8 9AG Tel: 0131 650 3230 Email: christopher.weir@ed.ac.uk

GRANT HOLDERS

Professor Stuart Ralston Centre for Genomic and Experimental Medicine Institute of Genetics & Molecular Medicine Western General Hospital Edinburgh EH4 2XU Tel: 0131 651 8743 Fax: 0131 651 1085 Email: stuart.ralston@ed.ac.uk	Dr Jennifer Walsh Clinical Senior Lecturer Metabolic Bone Centre Northern General Hospital Herries Road Sheffield S5 7AU Tel: 0114 271 4705 Email: j.walsh@sheffield.ac.uk
Dr M Kassim Javaid University Lecturer in Metabolic Bone Disease Nuffield Orthopaedic Centre, Windmill Road, Headington, Oxford, OX3 7HE Tel: 01865 227 374 Email: kassim.javaid@ndorms.ox.ac.uk	Professor Christopher Weir Centre for Population Health Sciences The University of Edinburgh Medical School, Teviot Place Edinburgh EH8 9AG Tel: 0131 650 3230 Email: christopher.weir@ed.ac.uk
Professor Bente Langdahl Consultant Physician Department of Endocrinology Aarhus University Hospital DK-8000 Aarhus C Denmark Tel +45-7846-7678 Email: bente.langdahl@aarhus.rm.dk	Ms Patricia Osborne Chief Executive Brittle Bone Society 30 Guthrie Street Dundee DD1 5BS Tel: 01382-204446 Email: patricia.osborne@brittlebone.org
Dr Wayne Lam Consultant Clinical Geneticist South East Scotland NHS Genetics Service Centre for Genomic and Experimental Medicine Institute of Genetics & Molecular Medicine Western General Hospital Edinburgh EH4 2XU Tel: 0131 537 1116 Wayne.lam@nhslothian.scot.nhs.uk Wayne.lam@ed.ac.uk	**Sheffield Teaching Hospitals NHS Trust** **Principal Investigator** Dr Jennifer Walsh Clinical Senior Lecturer Metabolic Bone Centre Northern General Hospital Herries Road Sheffield S5 7AU Tel: 0114 271 4705 Email: j.walsh@sheffield.ac.uk

PARTICIPATING SITES

NHS Lothian Health Board **Principal Investigator** Stuart H Ralston Professor of Rheumatology Rheumatic Diseases Unit Western General Hospital Edinburgh EH4 2XU Tel: 0131 651 3427 Email: stuart.ralston@ed.ac.uk	**University Hospitals Bristol NHS Trust** **Principal Investigator** Dr Shane Clarke Consultant Rheumatologist Bristol Royal Infirmary Upper Maudlin Street Bristol BS2 8HW Tel: 0117 342 7266 Email: s.clarke@bristol.ac.uk shane.clarke@UHBristol.nhs.uk
The Royal Liverpool Hospital **Principal Investigator** Dr Anna Daroszewska Honorary Consultant in Rheumatology and Clinical Biochemistry Department of Rheumatology Royal Liverpool University Hospital Prescott Street Liverpool L7 8XP Tel: 0151 794 9058 Email: A.Daroszewska@liverpool.ac.uk	**The Freeman Hospital Newcastle** **Principal Investigator** Dr Terry Aspray Consultant Physician Bone Clinic Freeman Hospital Newcastle upon Tyne. NE7 7DN Tel: 0191 213 7975 Email: t.aspray@newcastle.ac.uk
Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, Oxford **Principal Investigator** Dr M Kassim Javaid University Lecturer in Metabolic Bone Disease Nuffield Orthopaedic Centre, Headington, Oxford, OX3 7HE Tel: 01865 227 374 Email: kassim.javaid@ndorms.ox.ac.uk	**Queen Elizabeth Hospital Birmingham** **Principal Investigator** Prof Neil Gittoes Department of Endocrinology Queen Elizabeth Hospital Edgbaston Birmingham B15 2TH Tel: 0121 371 6940 Email: neil.gittoes@uhb.nhs.uk
Cambridge University Hospitals NHS Trust **Principal Investigator** Dr Ken Poole Consultant Rheumatologist Addenbrookes Hospital Cambridge CB2 0QQ Tel: 0141 451 6142 Email: kenneth.poole@nhs.net	**Principal Investigator** Dr Hrushikesh Divyateja Chemical Pathology Nottingham City Hospital Nottingham NG5 1PD Tel: 0115-969-1169 Email: Hrushikesh.Divyateja@nuh.nhs.uk

Robert Jones and Agnes Hunt Orthopaedic Hospital NHS Foundation **Principal Investigator** Dr Mark Garton Consultant Rheumatologist Robert Jones and Agnes Hunt Orthopaedic Hospital NHS Foundation Oswestry AY10 7AG Tel: 01691-404000 Email: Mark.Garton@rjah.nhs.uk **Nottingham University Hospitals NHS Trust**	**Aberdeen Royal Hospitals NHS Trust** **Principal Investigator** Dr Rosemary Hollick Consultant Rheumatologist Aberdeen Royal Infirmary Aberdeen AB25 2ZR Tel: 01224 438063 Email: rhollick@abdn.ac.uk
Norfolk and Norwich University Hospitals NHS Foundation Trust **Principal Investigator** Professor William D Fraser Faculty of Medicine and Health Sciences Bob Champion Research and Educational Building, James Watson Road, University of East Anglia Norwich NR4 7UQ Tel: 01603 597174 Email: w.fraser@uea.ac.uk	**Ninewells Hospital and Medical School** **Principal Investigator** Dr Ellen Malcolm Associate Specialist Department of Medicine Ninewells Hospital Dundee DD1 9SY. Tel: 01382-660111 Email: ellen.malcolm@nhs.net
Royal National Orthopaedic Hospital NHS Trust **Principal Investigator** Dr Richard Keen Consultant Rheumatologist RNOH Stanmore Brockley Hill Stanmore Middlesex HA7 4LP Tel: 020 8954 2300 Email: DrRichardKeen@aol.com	**Midlands Partnership NHS Foundation Trust** **Principal Investigator** Dr Zoe Paskins Haywood Community Hospital Haywood Road Staffordshire ST6 7AG Tel: 01782-673500 Email: z.paskins@keele.ac.uk
University Hospital Llandough **Principal Investigator** Dr Mike Stone University Hospital Llandough Penlan Road, Llandough, Penarth CF64 2XX Tel: 0209 2071 1711 Email: mikestone1959@gmail.com	**Manchester Royal Infirmary** **Principal Investigator** Professor Peter Selby Clinical Professor of Metabolic Bone Disease Centre for Endocrinology & Diabetes University of Manchester Manchester Royal Infirmary Oxford Road, Manchester ML13 9WL Tel: 0161-276-8917 Email: peter.selby@manchester.ac.uk

South Tees Hospitals NHS Foundation Trust **Principal Investigator** Dr Stephen Tuck James Cook University Hospital Marton Road Middlesborough TS4 3BW Tel: 01642 854757 Email: stephen.tuck@stees.nhs.uk	**Leicester Royal Infirmary** **Principal Investigator** Dr Prashanth Patel Head of Service Department of Chemical Pathology Sandringham Building Leicester Royal Infirmary LE1 5WW Tel: 0116 258 6550 Email: prashanth.patel@uhl-tr.nhs.uk
University Hospital Southampton **Principal Investigator** Professor Nick Harvey MRC Lifecourse Epidemiology Unit Southampton General Hospital Tremona Road Southampton SO16 6YD Tel: 023 8077 7624 Email: nch@mrc.soton.ac.uk	**Belfast Health and Social Care Trust** **Principal Investigator** Dr John R Lindsay Royal Victoria Hospital 274 Grosvenor Road Belfast BT12 6BA Tel: 028 9024 0503 Email: johnrlindsay@belfasttrust.hscni.net
Guys & St Thomas NHS Trust **Principal Investigator** Dr Geeta Hampson Consultant Physician Metabolic Bone Clinic Guy's Hospital Great Maze Pond London SE1 9RT Tel: 020 7188 7188 Email: Geeta.hampson@kcl.ac.uk	**Aintree University Hospital** **Principle Investigator** Dr Mashood Siddiqi Metabolic Bone Diseases Aintree University Hospital NHS Foundation Trust Aintree University Hospital Lower Lane Liverpool L9 7AL Tel: 0151 529 8703 Email: Mashood.siddiqi@aintree.nhs.uk
Queen Elizabeth University Hospital Glasgow **Principal Investigator** Dr Stephen Gallacher Consultant Physician Queen Elizabeth University Hospital 1345 Govan Road Glasgow G51 4TF Tel: 0141-201-1100 Email: Stephen.Gallacher@ggc.scot.nhs.uk	**St. Vincent's University Hospital, Dublin** **Principal Investigator** Dr Rachel Crowley Consultant Physician St Vincent's University Hospital Elm Park, Dublin 4 Republic of Ireland Tel: +353-1-6639822 Email: R.Crowley@st-vincents.ie

Aarhus University Hospital **Principal Investigator** Professor Bente Langdahl Aarhus University Hospital Clinical Medicine – Endocrinology and Metabolism C Tage-Hansens Gade 2 800 Aarhus C Denmark Tel: + 45 7846 7678 Email: Bente.langdahl@clin.au.dk	**Odense University Hospital** **Principal Investigator** Dr Pernille Hermann Endocrinology Odense University Hospital Kløvervænget 6 DK-5000 Odense C Denmark Tel: +45 2360 2366 Email: Pernille.hermann@rsyd.dk
Amsterdam University Medical Center **Principal Investigator** Dr Marelise Eekhoff Endocrinology Amsterdam University Medical Centre Dr Boelelaan 1117 1081 HV Amsterdam The Netherlands Tel: + 31 20 444 4444 *61729 Email: EMW.Eekhoff@vumc.nl	**Llandudno General Hospital** **Principle Investigator** Dr Kirsty MacLean The North Wales Bone Unit and Osteoporosis Service Llandudno General Hospital Betsi Cadwaladr University Health Board Llandudno Conwy LL30 1LB Tel: 01492 862356 Email: Kirsty.Maclean2@wales.nhs.uk
Hôpital Lariboisiére **Principal Investigator** Dr Martine Solal-Cohen Inserm U1132, University Paris-Diderot P7 and Department of Rheumatology Hôpital Lariboisiére 2 Rue Ambroise Paré 75010 Paris France Tel: + 33 1 49 95 63 58 Email: martine.cohen-solal@inserm.fr	**Hull Royal Infirmary** **Principle Investigator** Dr Deepa Narayanan Chemical Pathology and Metabolic Medicine Hull and East Yorkshire Hospitals NHS Trust Hull Royal Infirmaru Brocklehurst Building Anlaby Road Hull East Yorkshire HU3 2RW Tel: 01482 607743 Email: Deepa.Narayanan@hey.nhs.uk

CONTENTS

1 INTRODUCTION 13
1.1 BACKGROUND 13
1.2 RATIONALE FOR STUDY 13
2 STUDY OBJECTIVES 14
2.1 OBJECTIVES 14
2.1.1 Primary Objective 14
2.1.2 Secondary Objectives 14
2.2 ENDPOINTS 14
2.2.1 Primary Endpoint 14
2.2.2 Secondary Endpoints 14
3 STUDY DESIGN 14
4 STUDY POPULATION 15
4.1 NUMBER OF PARTICIPANTS 15
4.2 INCLUSION CRITERIA 15
4.3 EXCLUSION CRITERIA 15
4.4 CO-ENROLMENT 15
5 PARTICIPANT SELECTION AND ENROLMENT 16
5.1 IDENTIFYING PARTICIPANTS 16
5.2 CONSENTING PARTICIPANTS 17
5.3 SCREENING FOR ELIGIBILITY 17
5.4 INELIGIBLE AND NON-RECRUITED PARTICIPANTS 17
5.5 RANDOMISATION 17
5.5.1 Randomisation Procedures 17
5.5.2 Treatment Allocation 17
5.5.3 Emergency Unblinding Procedures 18
5.5.4 Withdrawal of Study Participants 18
6 INVESTIGATIONAL MEDICINAL PRODUCT AND PLACEBO 18
6.1 STUDY DRUG: IMP1 - Teriparatide 18
6.1.1 Study Drug Identification 18
6.1.2 Study Drug Manufacturer 18
6.1.3 Marketing Authorisation Holder 18
6.1.4 Labelling and Packaging 18
6.1.5 Storage 19
6.1.6 Summary of Product Characteristics or Investigators Brochure 19
6.2 STUDY DRUG: IMP2 - Zoledronic acid 19
6.2.1 Study Drug Identification 19
6.2.2 Study Drug Manufacturer 19
6.2.3 Marketing Authorisation Holder 19
6.2.4 Labelling and Packaging 19
6.2.5 Storage 19
6.2.6 Summary of Product Characteristics or Investigators Brochure 20
6.3 STUDY DRUG: IMP3 - Standard Care 20
6.3.1 Study Drug Identification 20
6.3.2 Study Drug Manufacturer 20
6.3.3 Marketing Authorisation Holder 20
6.3.4 Labelling and Packaging 20

6.3.5 Storage 20
6.3.6 Summary of Product Characteristics or Investigators Brochure 20

6.4 PLACEBO 20
6.5 DOSING REGIME 20
6.6 DOSE CHANGES 21
6.7 TEMPORARY AND PERMANENT TPTD STOPS 21
6.8 PARTICIPANT COMPLIANCE 21
6.9 OVERDOSE 22
6.10 OTHER MEDICATIONS 20
6.10.1 Non-Investigational Medicinal Products 22
6.10.2 Permitted Medications 22
6.10.3 Prohibited Medications 22

7 STUDY ASSESSMENTS 23
7.1 ASSESSMENT OVERVIEW 23
7.2 SAFETY ASSESSMENTS 23
7.3 STUDY ASSESSMENTS 24
BASELINE VISIT 24
REVIEW VISITS FOR PARTICIPANTS RECEIVING TPTD 25
FOLLOW UP VISIT AT 12 MONTHS 26
FOLLOW UP VISIT AT 24 MONTHS 26
END OF STUDY VISIT 27
ASSESSMENTS FOR FRACTURE 28
OPTIONAL CONTACTS 28

8 DATA COLLECTION 28

9 STATISTICS AND DATA ANALYSIS 29
9.1 SAMPLE SIZE CALCULATION 29
9.2 PROPOSED ANALYSES 29

10 ADVERSE EVENTS 30
10.1 DEFINITIONS 31
10.2 IDENTIFYING AEs AND SAEs 31
10.3 RECORDING AEs AND SAEs 31
10.4 ASSESSMENT OF AEs AND SAEs 32
10.4.1 Assessment of Seriousness 32
10.4.2 Assessment of Causality 32
10.4.3 Assessment of Expectedness 32
10.4.4 Assessment of Severity 32
10.5 REPORTING OF SAEs/SARs/SUSARs 33
10.6 REGULATORY REPORTING REQUIREMENTS 33
10.7 FOLLOW UP PROCEDURES 34

11 PREGNANCY 34

12 TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS 34
12.1 TRIAL MANAGEMENT GROUP 34
12.2 TRIAL STEERING COMMITTEE 34
12.3 DATA MONITORING COMMITTEE 35
12.4 INSPECTION OF RECORDS 35
12.5 RISK ASSESSMENT 35

12.6 STUDY MONITORING AND AUDIT 35
13 GOOD CLINICAL PRACTICE 35
13.1 ETHICAL CONDUCT 35
13.2 REGULATORY COMPLIANCE 35
13.3 INVESTIGATOR RESPONSIBILITIES 36
13.3.1 Informed Consent 36
13.3.2 Study Site Staff 36
13.3.3 Data Recording 36
13.3.4 Investigator Documentation 36
13.3.5 GCP Training 36
13.3.6 Confidentiality 37
13.3.7 Data Protection 37
14 STUDY CONDUCT RESPONSIBILITIES 37
14.1 PROTOCOL AMENDMENTS 37
14.2 PROTOCOL VIOLATIONS AND DEVIATIONS 37
14.3 SERIOUS BREACH REQUIREMENTS 37
14.4 STUDY RECORD RETENTION 37
14.5 END OF STUDY 37
14.6 CONTINUATION OF DRUG FOLLOWING THE END OF STUDY 37
14.7 INSURANCE AND INDEMNITY 37
15 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS 39
15.1 AUTHORSHIP POLICY 39
15.2 PUBLICATION 39
15.3 PEER REVIEW 39
16 REFERENCES 39
17 APPENDICES 42

PROTOCOL APPROVAL

EudraCT number 2016-003228-22

Signatures

Stuart H Ralston Chief Investigator	Signature	25TH MAR 2019 Date
Christopher Weir Trial Statistician	Signature	25/03/2019 Date
Fiach O'Mahony Sponsor(s) Representative	Signature	19 March 2019 Date
Professor Phil Conaghan Chair, Trial Steering Committee	Signature	19-MAR-2019 Date

For multi-site trials, the Principal Investigator must sign below to document that the protocol has been read and understood.

	Name			
Principal Investigator	Signature	Site		Date

LIST OF ABBREVIATIONS

ACCORD	Joint office for University of Edinburgh and NHS Lothian – Academic and Clinical Central Office for Research & Development
AE	Adverse Event
AR	Adverse Reaction
BBS	Brittle Bone Society
BMD	Bone Mineral Density
BPI	Brief Pain Inventory
CI	Chief Investigator
COLIA1	Collagen type IA1 gene
COLIA2	Collagen type IA2 gene
CRF	Case Report Form
CTA	Clinical Trial Agreement
CV	Curriculum Vitae
DMC	Data Monitoring Committee
ECTU	Edinburgh Clinical Trials Unit
EDTA	Ethylene diamine tetracetic acid
eGFR	Estimated Glomerular Filtration Rate
EME	Efficacy and Mechanism Evaluation
EuroQol5D	EuroQol5D
HAQ	Health Assessment Questionnaire
GCP	Good Clinical Practice
IB	Investigator Brochure
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
ISF	Investigator Site File
IUD	Intrauterine Device
IUS	Intrauterine System
IV	Intravenous
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NIMP	Non Investigational Medicinal Product
OI	Osteogenesis Imperfecta
PI	Principal Investigator
PIC	Patient identification centre
PQSI	Pittsburgh Sleep Quality Index
PTH	Parathyroid Hormone
QA	Quality Assurance
R&D	Research and Development
REC	Research Ethics Committee
RUDY	A study of Rare Diseases in bone, joint and vasculature
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SF-36	Short Form Health Survey
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TPTD	Teriparatide

TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
WOCBP	Women of Childbearing Potential
ZA	Zoledronic acid

SUMMARY

STUDY TITLE	Randomised trial of Teriparatide followed by Zoledronic acid versus standard care to prevent fractures in adults with Osteogenesis Imperfecta (OI)
SHORT TITLE AND ACRONYM	Treatment of Osteogenesis Imperfecta with Parathyroid hormone and Zoledronic acid (TOPaZ)
BACKGROUND	Osteogenesis imperfecta is an inherited skeletal disorder characterised by increased risk of fragility fractures. Bisphosphonates are frequently prescribed for adult patients with OI with the aim of preventing fractures but the evidence base for efficacy is poor. Recent evidence suggests that the bone anabolic agent teriparatide (TPTD) increases bone mineral density (BMD) and may have the potential to prevent fractures in osteogenesis imperfecta
STUDY OBJECTIVES	Primary Objective To investigate if a two-year course of TPTD followed by antiresorptive therapy with a single infusion of zoledronic acid (ZA) in adults with OI reduces the proportion of patients who experience a fracture as compared with standard care Secondary Objectives To investigate if a two-year course of TPTD followed by antiresorptive therapy with a single infusion of ZA in adults with OI reduces the total number of fractures, reduces the risk of vertebral fractures; or affects bone pain, quality of life and functional status as compared with standard care. Mechanistic Objective To understand which baseline characteristics of adults with OI, such as age, clinical subtype of OI, genetic diagnosis, bone turnover, BMD, and previous treatment influences the occurrence of fractures and/or the response to treatment
STUDY POPULATION	Adult patients with a clinical diagnosis of OI who are willing and able to give informed consent and who do not have contraindications to the study medications.
STUDY TREATMENT	Participants will be randomised in a 1:1 ratio to receive standard care for the duration of the study or TPTD for 2 years followed by an infusion of ZA or another antiresorptive agent in the event that ZA is contraindicated.
STUDY ASSESSMENTS	The baseline assessment will include dual energy x-ray absorptiometry (DEXA), spine x-rays, safety bloods, medical and fracture history, pain (brief pain inventory, BPI) and quality of life (SF36, HAQ, EQ5D, PSQI). Blood will be taken for genetic analysis and for analysis of biochemical markers of bone turnover. In some centres, a high resolution quantitative CT scan (HRQCT) of the wrist and tibia will be performed. Participants will be seen after 12 months when bloods, questionnaires and HRQTC will be repeated; at 24 months when bloods, questionnaires, DEXA and HRQCT will be repeated. At the end of the study participants will undergo DEXA, spine x-rays, HRQCT and bloods and questionnaires will be repeated. Information on adverse events and fractures will be collected throughout the study and participants suspected to have fractures will have x-ray or other imaging to confirm the presence of fractures.

1 INTRODUCTION

1.1 BACKGROUND

Osteogenesis imperfecta (OI) is an inherited skeletal disorder with a prevalence of about 11/100,000 which is characterised by an increased risk of fragility fractures (1). It is most commonly caused by mutations of the *COLIA1* or *COL1A2* genes which result in the production of collagen which is abnormal or present in reduced amounts although mutations in several other genes have been identified over recent years which can result in the same clinical phenotype (2).

The fracture risk in OI is at least an order of magnitude above that in patients with osteoporosis. Affected individuals are at increased risk of fragility fractures throughout life but the highest rates of fracture are during childhood and above the age of 50 years (3). While affected individuals suffer tens or hundreds of fractures during their lifetime (2-4) there is relatively little information on fracture rate in prospective studies. A survey of adult patients with OI recently carried out in collaboration with the brittle bone society revealed that 79% of subjects had suffered a fracture during the previous 5 years, equivalent to an annualised fracture rate of about 16%. This is in keeping with data from randomised trials and observational studies, which on average, have reported an annualised fracture rate of about 17% (4-9).

Bone mineral density (BMD) is variable in patients with OI (10) and the increased risk of fracture is observed even in patients with normal BMD or osteopenia (3;4). However, a cohort study in Norway found that patients with BMD values in the osteoporotic range (T-score <-2.5) had a 3-fold higher rate of fractures than those with normal BMD or osteopenia (4). This is an important observation since it provides proof-of-concept that strategies aimed at increasing bone mass might reduce fracture rate in OI.

Bisphosphonates are frequently prescribed for patients with OI with the aim of preventing fractures but the evidence base for efficacy is poor. Previous Cochrane reviews and meta-analysis of trials in OI have concluded that while bisphosphonates consistently increased BMD in both children and adults the effects on fracture risk are uncertain (11-13). It remains unclear why the increase in BMD resulting from bisphosphonate treatment has not been associated with a consistent reduction in fractures. However one explanation might be that the increase in BMD that occurs with bisphosphonates is due mainly to increased mineralisation of bone, rather than an increase in the amount of bone tissue (14).

Recently a randomised placebo controlled trial with the bone anabolic agent teriparatide (TPTD) has been conducted in adults with OI with encouraging results (9). Not only did TPTD increase BMD when compared with placebo but the odds ratio of fracture was reduced in the active treatment arm, but not significantly (0.73; 95% CI 0.28-1.90). This study had a short duration of follow up however, and was not powered to detect a reduction in fracture risk. Another observational study of TPTD also showed encouraging results in OI patients previously treated with bisphosphonates but fracture data were not reported (5).

1.2 RATIONALE FOR STUDY

In view of the inconclusive results that have been obtained with bisphosphonates in the treatment of OI (12;13;15).and the encouraging preliminary results that have been obtained with TPTD (9), the aim of the present study is to determine whether TPTD, followed by antiresorptive therapy with a single infusion of zoledronic acid (ZA) to maintain the increase in bone mass reduces the risk of fracture in adults with OI as compared with standard care. The prolonged antiresorptive effect of ZA means that a single infusion is expected to maintain the increase in BMD for at least three years (16;17).

2 STUDY OBJECTIVES

2.1 OBJECTIVES

2.1.1 Primary Objective

The primary objective will be to investigate if a two-year course of TPTD followed by antiresorptive treatment with a single infusion of ZA in adults with OI reduces the proportion of patients who experience a fracture as compared with standard care.

2.1.2 Secondary Objectives

Secondary objectives will be to determine if treatment influences the total number of fractures, bone pain, quality of life, functional status and adverse events. In addition, the study will have a mechanistic objective which is to gain understanding of how the baseline characteristics of adults with osteogenesis imperfecta such as age, clinical subtype of OI, genetic diagnosis, BMD, and previous treatment, influence the risk of fractures; other secondary endpoints, adverse events and the response to treatment

2.2 ENDPOINTS

2.2.1 Primary Endpoint

The proportion of participants experiencing a clinical fracture validated by x-ray or other imaging.

2.2.2 Secondary Endpoints

The total number of clinical fractures experienced by participants validated by x-ray or other imaging.

The number of incident vertebral fractures assessed by imaging of the thoracic and lumbar spine.

The total number of fractures experienced by participants defined as the combination validated clinical fractures and vertebral fractures and fractures reported by participants, where imaging was not performed, not feasible or where the results were inconclusive.

Bone pain assessed by the brief pain inventory (BPI); quality of life as assessed by the SF36 questionnaire; Pittsburgh sleep quality questionnaire (PSQI) and functional status as assessed by the health assessment questionnaire (HAQ) and EuroQol5D (EQ5D) assessment tools, and adverse events.

To evaluate the relationship between patient demographics, clinical features of OI, bone density values at baseline, type of genetic mutation and biochemical markers of bone turnover and fracture occurrence OI and the response to treatment.

3 STUDY DESIGN

Prospective, open label randomised controlled trial with centralised adjudication of the fracture endpoints by blinded assessors. Participants will be randomised in a 1:1 ratio to receive treatment with TPTD for 2 years followed by an infusion of ZA or to receive standard care for the duration of the study. All participants will be followed up for a total duration of between 2 and 5 years.

4 STUDY POPULATION

4.1 NUMBER OF PARTICIPANTS

The sample size will be 380 patients, with 190 in each treatment group.

4.2 INCLUSION CRITERIA

- Adult patients age 18 years and over with a clinical diagnosis of OI
- Patients willing and able to consent and comply with the study protocol.

4.3 EXCLUSION CRITERIA

- Current or previous treatment with an investigational (non-licensed experimental) drug with effects on bone metabolism.
- Contraindication to TPTD or ZA
- Women of childbearing potential not using highly effective methods of contraception (see below)
- Pregnancy
- Women that are breastfeeding
- Age <18 years

Women of childbearing potential (WOCBP) can be enrolled into the study but will be required to use highly effective methods of contraception (as defined by the HMA Clinical Trial Facilitation Group recommendations) before, during the trial if they are being treated with TPTD or bisphosphonates. Examples of highly effective contraception include:

- Established use of oral, injected or implanted hormonal methods of contraception.
- Placement of an intrauterine device (IUD) or intrauterine system (IUS).
- Bilateral tubal occlusion
- Vasectomised partner
  True abstinence. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Barrier methods of contraception (condom or occlusive cap (diaphragm or cervical/vault caps with or without spermicidal foam/gel/film/cream/suppository) are not considered to be highly effective methods of contraception.

4.4 CO-ENROLMENT

Co-enrolment will be permitted for potential participants have already been enrolled in studies that involve collection of data such as questionnaires and tissue samples such as Biobank UK and similar epidemiological studies. Participants that have consented to take part in the TOPaZ study will also be permitted to enrol in other observational studies provided that the burden of visits would not compromise the integrity of the TOPaZ study. Co-enrolment with a non-interventional research (e.g. sample only, questionnaire studies) will not require any formal documentation or authorisation from the Sponsor.. Co-enrolment between TOPaZ and another CTIMP study may be permitted according to ACCORD Co-enrolment Policy (POL008). At the screening visit participants will be asked if they are taking part in any other studies. During the trial, participants will also be asked to inform the study team if they have been approached to take part in any other studies.

5 PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

The main route of recruitment to the study will be through the potential participants' normal NHS care providers. Potential participants will be approached directly as they attend for routine outpatient clinic visits or by telephone or letter following review of clinic lists. A selected number of sites will contact patients using an invitation letter together with a trial-branded pen as part of a Study Within A Trial (SWAT).

Information about the trial will also be posted on the website of the Brittle Bone Society (BBS), a patient support organisation and communicated through newsletters and emails of the BBS. Information will also be provided through the RUDY project; an ongoing national cohort of patients with rare bone diseases who consent to be contacted about future ethically approved studies.

Potential participants, who become aware of the study through the BBS, RUDY or through other routes such as word of mouth from affected relatives, will be invited to contact the research team at the co-ordinating centre or their nearest study centre if they are interested in taking part. Following such contact, they will be provided with information about the trial.

We will set up several study centres spread across the UK,Republic of Ireland, Denmark, the Netherlands and France (summarised on pages 4-6). In addition, patient identification centres (PIC) in which patients with OI attending district general hospitals will be established. The PIC will provide potentially eligible patients attending routine clinics information about the study. Potential participants that express an interest in the study will then be offered referral to one of the main study centres.

Reasonable travel expenses (i.e. not first-class train travel) will be covered for all participants. Sites may recruit from a wide geographical area if potential participants are able and willing to comply with the study protocol by attending scheduled visits.

By prior arrangement with the TOPaZ Trial Office, sites may recruit participants who, for logistic reasons, are unable to visit study centres for TPTD resupply visits on the following conditions:

i) TPTD can be stored and dispensed from a local hospital pharmacy with GCP training

ii) local hospital pharmacies should adhere to the same procedures as recruiting site pharmacies in terms of IMP receipting, dispensing and accountability

iii) remote contact with participants by the study team via telephone interview or email is fully documented (as per a standard visit) in eCRF and in medical notes

iv) shipments of Trial TPTD from recruiting site pharmacies to local hospital pharmacies be temperature controlled with either records provided (if using system already in place) or Trial Office temperature monitors provided.

5.2 CONSENTING PARTICIPANTS

Participants will be supplied with an information sheet from a member of the study team containing details of the study aims and procedures prior to enrolment in the study. Once they have had adequate time (at least 24 hours) to consider the information sheet and ask questions written consent will be sought from trained research nurses or doctors that are involved in the study. The investigator will ensure informed consent is evidenced in writing, dated and signed, or otherwise marked, by that person so to indicate their consent. If the person is unable to sign or to mark a document so as to indicate their consent, it should be given orally in the presence of at least one impartial witness and recorded in writing.

Participants will be given the option to consent separately to genetic testing and being informed of the results of the genetic tests.

Following informed consent, participants personal details including hospital numbers and NHS numbers will be held by members or the research team at study sites and by members of the study team at the co-ordinating centre to ensure that the study team can make contact with participants to feedback the results of the genetic testing, to organise study visits, to obtain radiographs of participants who are suspected to have suffered a fracture and to obtain information on adverse events.

5.3 SCREENING FOR ELIGIBILITY

Prior to any study specific screening investigations, informed consent must be given by the patient. The procedures and investigations that will be performed at the baseline visit prior to randomisation are listed in section 7.1.

5.4 INELIGIBLE AND NON-RECRUITED PARTICIPANTS

An anonymised log will be kept for patients who were screened for the study but subsequently found to be ineligible or not recruited.

5.5 RANDOMISATION

5.5.1 Randomisation Procedures

Randomisation will be performed centrally by Edinburgh Clinical Trials Unit using a secure website thus concealing the allocation sequence. Randomisation will be performed by research staff at study sites who will log onto the randomisation website with a username and password supplied by the co-ordinating centre. Participants will be randomised to receive treatment with TPTD/ZA or standard of care in a 1:1 ratio. Minimisation will be employed to balance the treatment groups for variables that might influence fracture occurrence. These include:

- Clinical fracture during the two years prior to randomisation
- Clinical subtype of OI (type I or others)
- Gender
- Lowest BMD T score at spine or hip (or Z-score aged 18-21) ≤-2.5; or >-2.5.
- Age (≤50; >50)
- Bisphosphonate at entry or within 2 years prior to randomisation

The minimisation algorithm will incorporate a computer-generated random number element to maintain unpredictability of treatment allocation.

If DEXA is not feasible for technical reasons such as in patients with metalwork in situ as the result of previous fractures or because of multiple vertebral fractures they will be assumed to have a T score of <-2.5 for the purposes of minimisation.

Participants and local investigators will not be blinded to treatment allocation. However, certain members of the research team at the co-ordinating centre and the researchers responsible for adjudicating fractures will be blinded to treatment allocation. The names of the research staff at the co-ordinating centre that will not have access to the treatment allocation codes will be recorded in the trial master file.

Once a participant has been randomised they will be given a card to indicate they are on the trial. Participants will be instructed to show this to any healthcare professional involved in their care who is not involved in the study

5.5.2 Treatment Allocation

Active treatment group:
TPTD 20mcg daily, given subcutaneously using a self-administered injection device for two years followed by a single intravenous infusion of ZA 5mg. If TPTD given for < 12 months no ZA infusion is required.

Bisphosphonates, denosumab and strontium ranelate will be stopped in the active treatment group at baseline and prohibited during treatment with TPTD since these may alter the therapeutic response to TPTD (18). Bisphosphonates will be prohibited following treatment with ZA for at least 12 months to avoid over suppression of bone turnover. If for any reason administration of ZA is not feasible, such as poor venous access, another antiresorptive agent (including - in this instance only - denosumab) may be administered as an alternative means of maintaining the increase in BMD at the end of TPTD treatment. Before commencing an alternative to ZA, local investigators should fully discuss the choice of agent and the reason for not using ZA with the co-ordinating centre.

Standard care group;
Participants in the standard care group may continue with existing bone modifying treatment (i.e. bisphosphonate treatment) or be given no active bone modifying treatment, according to the clinical judgement of the local investigator. Bisphosphonates may be continued, stopped or started during the study at the discretion of the local investigator. Other bone modifying drugs may also be given at the discretion of the local investigator with the exception of teriparatide and investigational (experimental) agents with effects on bone metabolism.

Calcium and vitamin D supplements and/or vitamin D supplements and hormone replacement therapy can be given in both groups if clinically indicated according to normal clinical practice and at the discretion of the local investigator. Calcium and vitamin D supplements are included within the SPC as Non-Investigational Medicinal Products (NIMPs).

5.5.3 Emergency Unblinding Procedures

Not applicable. The study is open label.

5.5.4 Withdrawal of Study Participants

Participants will be free to withdraw from the study at any point or a participant can be withdrawn by the investigator. If withdrawal occurs the primary reason for withdrawal should be documented in the participant's Case Report Form (CRF). Participants who wish to withdraw will be provided with the following options.

- Withdrawal from treatment but remaining in follow up
- Withdrawal from treatment and follow up (but with retention of data up to the time of withdrawal for use in analysis)

Reasons for withdrawing from active treatment may include:
- Further participation is considered by the attending clinician not to be in the patient's best interest
- Development of renal impairment or other medical condition that would represent a contraindication to continued treatment with TPTD or bisphosphonates.

6 INVESTIGATIONAL MEDICINAL PRODUCT AND PLACEBO

6.1 STUDY DRUG: IMP1 - Teriparatide

6.1.1 Study Drug Identification

Teriparatide (1-34 fragment of PTH) 20 micrograms daily by subcutaneous injection. Needles for Forsteo pens are not provided and compatible needles should be supplied by participating sites.

6.1.2 Study Drug Manufacturer

Teriparatide: Forsteo manufactured by Eli Lilly and Company Limited

6.1.3 Marketing Authorisation Holder

Eli Lilly Nederland B.V., Papendorpseweg 83, 3528 BJ Utrecht, The Netherlands,

6.1.4 Labelling and Packaging

Teriparatide: Forsteo will be supplied by Eli Lilly and Company from commercial stock to sites via PCI Pharma Services. In the UK and Republic of Ireland, there will be no modifications to original packaging aside from the addition of reduced labelling with regulatory approval to indicate that they are for use within the TOPaZ clinical trial only. A trial-specific dispensing label should be applied at site prior to dispensation to participants. In the Netherlands, France and Denmark then original packaging will be replaced with plain packaging and Annex 13 compliant labelling in the local language applied by PCI Pharma Services (translation by Andiamo Language Services Ltd).

6.1.5 Storage

Storage and dispensing of the TPTD will be undertaken by research pharmacies in the participating centres in accordance with the Pharmacy Manual provided. TPTD must be stored in a refrigerator (2°C-8°C at all times). The pen should be returned to the refrigerator immediately after use. Do not freeze.

6.1.6 Summary of Product Characteristics or Investigators Brochure

The SPC for Forsteo is included within the trial representative set of SPC provided. The RSI can be found in section 4.8 of the Forsteo SPC.

6.2 STUDY DRUG: IMP2 – Zoledronic acid

6.2.1 Study Drug Identification

Zoledronic Acid 5 mg/100ml solution for infusion. Any licensed preparation of zoledronic acid may be employed to deliver the required dose but vial sharing is only permitted if used by trial participants attending for infusions on the same day.

6.2.2 Study Drug Manufacturer

Any preparation ZA which has marketing authorisation in the UK,the Republic of Ireland, Denmark, the Netherlands and France may be employed in the active treatment group.

6.2.3 Marketing Authorisation Holder

Not applicable

6.2.4 Labelling and Packaging

A trial-specific dispensing label should be applied at site prior to dispensation of ZA.

6.2.5 Storage

Storage and dispensing of the ZA will be undertaken by research pharmacies in the participating centres but alternative arrangements may be made for by prior arrangement with the TOPaZ trial office.

6.2.6 Summary of Product Characteristics or Investigators Brochure

A representative SmPC be provided is provided in the SPC pack. The RSI can be found in section 4.8 of the Zoledronic Acid SPC.

6.3 STUDY DRUG: Standard Care

6.3.1 Study Drug Identification

Standard care: Any licensed preparation of bisphosphonate may be employed, at doses which are normally used in routine practice for the treatment of osteogenesis imperfecta. Other bone active drugs including denosumab may also be given at the discretion of the local investigator.

6.3.2 Study Drug Manufacturer

Any bisphosphonate which has marketing authorisation in the UK, the Republic of Ireland, Denmark, the Netherlands and France will be permitted in the standard care group.

6.3.3 Marketing Authorisation Holder

Not applicable.

6.3.4 Labelling and Packaging

No specific arrangements are planned for labelling of the other Investigational Medicinal Products since we will use licensed medicinal products that are currently available in the UK in both treatment groups with a posology and mode of administration that is similar to the licensed indication of osteoporosis.

6.3.5 Storage

Dispensing of bisphosphonates and other medications in the standard care group will be undertaken by community pharmacies or hospital pharmacies using local internal procedures, with details recorded by site staff in the eCRF.

6.3.6 Summary of Product Characteristics or Investigators Brochure

Representative SPCs are provided in the SPC pack. The representative RSIs for standard care comparators can be found in section 4.8 of the appropriate SPC.

6.4 PLACEBO

No applicable

6.5 DOSING REGIME

The dosing regimen for TPTD in patients of ≥30Kg will be 20mcg daily given by subcutaneous injection for 24 months. Participants randomised to TPTD will be instructed that the TPTD needs to be stored in a refrigerator and will be taught how to self-administer the injection. Participants will be supplied with needles, a coolbag and gel packs and a sharps bin to store used needles and will be instructed to return these to the research team or pharmacy team at participating centres when full or at the end of study for disposal. Participants will be asked about adherence to the medication on returning the used pens to the study centres and will be asked to keep a study-specific 'pen diary'. The used pens will be disposed of by the pharmacies at participating centres according to local procedures and used sharps by either the research teams or pharmacies (depending on local practices).

After completing the two years of TPTD treatment, the patients in the active treatment arm will receive an infusion of ZA 5 mg intravenously over not less than 15 minutes administered by qualified staff at the participating sites within 4 weeks of the last TPTD dose (or an alternative antiresorptive agent – including denosumab in these circumstances only - if ZA contraindicated).

In the event that TPTD therapy needs to be discontinued before 12 months for any reason, the participant will not be given ZA on termination of TPTD therapy and instead will revert to receiving standard care.

Subjects that receive TPTD therapy for 12 months or more but less than 24 months will be given an infusion of ZA 5mg intravenously (or an alternative antiresorptive agent) as described above within 4 weeks of the last TPTD dose.

6.5.2 Dosing regimen for low body weight subjects

For subjects with a body weight ≤30kg the dose of TPTD will be reduced to 20mcg given twice weekly by subcutaneous injection for 24 months. Treatment will be followed by an infusion of ZA in a dose of 0.10 mg/Kg over 15 minutes within 4 weeks of the last TPTD dose.

In the event that TPTD therapy needs to be discontinued before 12 months for any reason, the participant will not be given ZA on termination of TPTD therapy and instead will revert to receiving standard care

Low body weight subjects that receive TPTD therapy for 12 months or more but less than 24 months will be given an infusion of ZA in a dose of 0.10 mg/Kg (or an alternative antiresorptive agent) as described above within 4 weeks of the last TPTD dose.

In the event that administration of ZA is not feasible an alternative antiresorptive agent may be given to maintain the increase in BMD on discussion with the clinical team at the co-ordinating centre.

In the standard care group bisphosphonates will be used at standard doses and intervals using the posology employed in routine clinical practice for osteogenesis imperfecta.

If required, calcium and vitamin D supplements will be prescribed in standard doses and intervals according to routine clinical practice

6.6 TEMPORARY AND PERMANENT TPTD STOPS

It is permissible for participants to temporarily stop (defined as ≥ 3 consecutive days) TPTD during the treatment period for up to 6 weeks. If this occurs the duration of the interruption and reason will be logged in the trial database. An interruption of greater than 6 weeks will be considered a permanent discontinuation. Participants who permanently discontinue TPTD before 12 months will revert to receiving standard care (see 6.5). Those who receive 12

months or more will be invited to attend for a ZA infusion or treatment with an alternative antiresorptive agent within 4 weeks of stopping therapy as described in section 6.5.

If participants are going on holiday for 1-14 days they should check if facilities are available during their holiday for the pen to be stored in a refrigerator. If they are sure that refrigerator facilities are available, they should take the pen on holiday and continue the treatment as normal. If they think refrigerator facilities might not be available or are unsure they should leave the pen at home and resume treatment when they return and log the doses as having been missed. Site teams should record any such stops lasting more than 3 days on the eCRF as a temporary stop. For Trips of ≥ 14 days: If participants are planning longer trips then they should discuss with site teams, and if necessary with the TOPaZ Trial Office, to put in place arrangements to allow them to keep taking their TPTD as per schedule.

6.7 PARTICIPANT COMPLIANCE

Adherence to TPTD will be monitored during the study through monitoring of returned injection devices to pharmacies at the participating centres and by enquiring whether any injections were missed at study visits, in conjunction with a participant pen diary. This information will be recorded in the CRF. Checks for compliance with ZA will not be necessary since this drug will be administered by intravenous infusion by the research team. Adherence with standard care will be assessed by enquiring about medication taken at study visits, including an estimation of compliance from participants. Every time participants reach the end of a course of a bone-specific treatment within the standard care arm they should be asked by site teams to estimate how much of the course was taken (all, most, half the time, some or none). This information will be recorded on the CRF. No specific threshold will be defined for non-compliance since analysis of the data will be based on the intention to treat principle. For the per-protocol analysis data on actual compliance will be taken into account in the statistical analysis plan which will be agreed by the trial steering committee prior to database lock (see section 9.1).

6.8 OVERDOSE

There have been cases of medication error with TPTD where the entire contents (up to 800 mcg) of the teriparatide pen have been administered as a single dose. Events reported have included nausea, weakness/lethargy and hypotension. No fatalities associated with such overdoses have been reported. Teriparatide has also been administered in single doses of up to 100 micrograms and in repeated doses of up to 60 micrograms/day for 6 weeks. Potential adverse effects that might be expected include hypercalcaemia, orthostatic hypotension, nausea, vomiting, dizziness, and headache. In the event of overdose occurring supportive treatment will be given' including intravenous fluids to reduce serum calcium levels if this proves necessary.

There is no experience of overdose with zoledronic acid. The SmPC states that people who have received doses higher than those recommended should be carefully monitored. In the event of overdose leading to clinically significant hypocalcaemia, reversal may be achieved with supplemental oral calcium and/or an intravenous infusion of calcium gluconate. It is highly unlikely that any participant in this study will be given an overdose of Zoledronic acid since the infusions will be administered under controlled conditions by experienced staff.

We are unaware of any instances of acute overdose of bisphosphonates such as alendronic acid, risedronate, pamidronate and ibandronate which may be employed in the standard care arm. If this occurs supportive care will be given according to routine practice.

6.9 OTHER MEDICATIONS

6.9.1 Non-Investigational Medicinal Products

Medicinal products that are already being prescribed to participants as part of routine care will be continued during the trial. Calcium and vitamin D supplements may be prescribed in both

groups according to standard practice unless the attending clinician feels that dietary intake of calcium and vitamin D and/or sunlight exposure are adequate to meet the recommended intake of both nutrients. Representative reference safety information for calcium (Calcichew D3) and vitamin D (Fultium-D3) are included within the trial SPC pack as Non-Investigational Medicinal Products (NIMPs).

6.9.2 Permitted Medications

Participants will therefore be free to take all their usual medication during the study including HRT with the exception of the prohibited medications listed in Section 6.7.3

Any regularly used medications that are being taken at the start of study or commenced while a participant is on study will be documented on the CRF.

6.7.3. Prohibited Medications

Active treatment: During the phase of treatment with TPTD, the following drugs will be prohibited; bisphosphonates, denosumab, strontium ranelate, calcitonin and investigational (experimental) drugs with effects on bone metabolism. These drugs will also be prohibited within 12 months of receiving ZA to avoid over suppression of bone turnover. An exception would be if for any reason ZA cannot be given to maintain the increase in BMD following TPTD. In this case an alternative antiresorptive agent (including denosumab within this context only) may be given on discussion with the co-ordinating centre.

Standard care group: Teriparatide and investigational (experimental) drugs with effects on bone metabolism will be prohibited.

If a prohibited medication is taken in error during the study this will be noted as a protocol deviation and the prohibited medication will be stopped. Patients who receive prohibited medications will remain in the study. If the local investigator feels on clinical grounds that the prohibited medication requires to be continued the participant will be withdrawn from the study.

7 STUDY ASSESSMENTS

7.1 OVERVIEW

TABLE 1	Screening / Baseline & Randomisation Visit(s)	*Additional safety bloods for participants <30kg only*			TPTD Resupply Visits See page 23 for further details	6 & 18 month telephone call	12 month Visit 52 weeks	24 month Visit 104 weeks	Follow-up 6 monthly telephone call	End o Study Visit
		2 weeks	4 weeks	12 weeks						
Informed consent	X									
Inclusion/exclusion	X									
Demographic data	X									
Medical history	X									
Clinical exam	X						X	X		X
DEXA	X							X		X
Spine x-ray	X									X
HRQCT	X						X	X		X
Safety bloods	X	X	X	X			X	X		X
EDTA blood sample	X									

Serum blood sample	X						X	X		X
Urine pregnancy test	X							X		
Participant Questionnaire Pack	X						X	X		X
Training on treatment	X									
Issue of diary	X									
Diary data entry					X	X	X	X	X	X
TPTD accountability					X	X	X	X		
Adverse events					X	X	X	X	X	X
Medications check					X	X	X	X	X	X
ZA infusion								X		
Retrieval of incident fracture x-rays*						X	X	X	X	X

- Retrieval of x-rays may occur at any point throughout the trial as and when incident fractures are reported. Sites are encouraged to retrieve and upload images as soon as possible after the report of an incident fracture

7.2 SAFETY ASSESSMENTS

Blood will be taken and analysed in local laboratories for assessment of serum creatinine, serum calcium, albumin, serum total alkaline phosphatase (ALP) and eGFR and (if clinically indicated) serum 25(OH)D prior to starting study medication to ensure there is no contraindication to TPTD or bisphosphonate therapy. Blood results from ≤ 3 months prior to the date of consent will be accepted as being valid for the Baseline Visit unless there has been an intercurrent illness which in the opinion of the local investigator necessitates that the bloods be repeated. Creatinine clearance will also be calculated within the trial database at baseline, 12 months 24 months and end of trial visits based on age, serum creatinine and body weight using the Cockcroft-Gault formula (20). Safety bloods must be checked prior to the ZA infusion (on the same day or within the previous 3 months unless there has been an intercurrent illness which would, as above, necessitate that bloods be repeated) at the 24-month visit (or before if TPTD stopped earlier) to ensure that there is no contraindication to ZA. Elevated serum calcium and ALP occur commonly in patients treated with TPTD and no action is required if this is indicated by the safety bloods collected at study visits or intervening periods. In the event of the development of impaired renal function with an eGFR ≤ 35 or moderate to severe hypercalcaemia (serum adjusted calcium >3.2mmol/l), study sites should contact the central coordinating centre for advice.

Investigators at site may choose to carry out more frequent safety blood tests. These tests will not be recorded on the eCRF but if they are performed, the results should be filed in the participants medical records. Any abnormal blood test results that are considered clinically significant by the local Investigator should be reported as Adverse Events on the trial database.

Pregnancy tests will be performed at the baseline visit in women of childbearing potential. Additionally, a pregnancy test will be performed at 24 months prior to the infusion of ZA in women of childbearing potential. Further pregnancy tests may be performed at any time at the discretion of the local investigator if they have reason to believe that a female participant has become pregnant despite taking adequate contraceptive measures.

Participants with body weight <30kg who are randomised to receive TPTD will undergo additional safety blood testing with measurements of serum calcium, albumin and creatinine after 2 weeks, 4 weeks and 12 weeks after the first injection. Thereafter the frequency of monitoring will revert to that for subjects of body weight ≥30kg unless the investigator chooses to carry out more frequent safety blood tests. The results of these additional tests will not be logged on the trial database but will be filed in the medical record. Any abnormal results deemed clinically significant will be logged as adverse events on the trial database.

7.3 STUDY ASSESSMENTS

BASELINE VISIT

At the baseline visit, participants will be provided with information about the study and invited to take part by providing written informed consent. Following provision of the information about the study participants will be advised that they can take as much time (and at least 24 hours) as they need to decide whether or not to take part in the study. Following completion of the baseline investigations there will be a window of 14 days during which randomisation should be completed and treatment commenced.

- **Demographics:** After consent has been obtained, information will be collected on demographics including date of birth, gender, smoking, alcohol intake, dietary calcium intake estimated by food frequency questionnaire, past medical history, family history of osteogenesis imperfecta, previous fractures, use of a hearing aid, current medications and current and previous bone active medications. In women, information will be collected on age at menarche, menopausal status and age at menopause.

- **Clinical examination:** Participants will undergo a clinical examination recording height and weight. The presence of bone deformity will be noted. Deformity will be recorded on the basis of the region involved; right and left lower limbs; pelvis, spine, rib cage, right and left upper limbs and skull. For each region the local investigator will be asked to grade deformity a 4-point scale at each site assessed: 0 = no deformity; 1=mild deformity; 2 = moderate deformity; 3=severe deformity. The presence or absence of blue sclerae and dentinogenesis imperfecta as assessed clinically will be noted.

- **DEXA:** Participants will undergo a bone mineral density scan using dual x-ray absorptiometry of the spine and hip by DEXA according to standard techniques, unless the local investigator feels that DEXA would not be feasible or informative (for example in patients with severe OI and multiple skeletal deformities or those with metalwork in situ that would preclude DEXA). If a DEXA scan has been performed within ≤ 6 months from the baseline visit this will be accepted as valid for the baseline assessment unless the patient has received bone active treatment during the intervening period.

- **Spine x-ray:** Lateral radiographs will be performed of the thoracic and lumbar spine to detect prevalent vertebral fractures. If a spine radiograph has been performed within ≤ 6 months from the baseline visit this will be accepted as valid for the baseline assessment unless the patient has received bone active treatment during the intervening period.

- **HRQCT:** Patients who are attending centres with access to high resolution CT equipment will have the option of having a high resolution quantitative CT (HRQCT) scan of the wrist and tibia.

- **Research bloods:** A sample of venous blood (2 x 5ml) will be collected into EDTA tubes for DNA extraction and genetic analysis. These will be sent immediately by first class post at ambient temperature to the University of Edinburgh Bone Research Laboratory. Another sample of up to 10ml will be collected and allowed to clot. Serum will be separated on site and 2 x 1ml aliquots prepared. These will be stored frozen at -70°c or below at the study site and shipped on dry ice to the University of Edinburgh Bone Research Laboratory where they will be stored at -70°c or below until they are used for analysis of biochemical markers of bone turnover. The date and time of taking the blood samples will be recorded on the CRF.

- **Safety bloods:** As described in Section 7.2. a sample of venous blood will be collected and analysed locally by laboratories at participating centres for serum

creatinine, calculation of eGFR, serum calcium, albumin, serum total alkaline phosphatase (ALP) and (if clinically indicated) serum 25(OH)D.

- **Urine pregnancy test:** All women of childbearing potential (WOCBP) defined as women who are premenopausal who have not been sterilised will require a negative urine pregnancy test prior to study inclusion.

- **Participant Questionnaire Pack:** Questionnaires will be completed for SF36, HAQ, EQ5D, PSQI and the brief pain inventory (BPI).

  Participant training: Participants allocated to the active treatment group (TPTD/ZA) will be trained in use of the injection device and given instructions on how to store the device.
- **Issue of Diary:** Participants will be issued with a diary to record visits made to their general practitioner, outpatient visits to hospital and in-patient hospital admissions. The date of the event and reason for seeking healthcare advice will be recorded. The occurrence of suspected fractures will also be recorded in the patient diary. The date and site of the suspected fracture will be recorded. Participants will be instructed to seek medical advice and undergo x-ray examination if they suspect they have suffered a fracture, in keeping with normal clinical practice.

REVIEW VISITS FOR PARTICIPANTS RECEIVING TPTD

Participants randomised to the active arm and receiving TPTD will be asked to attend the study centre at set intervals as set out in Table 2 below in order to collect new supplies of drug and to return used injection devices and sharps. During this visit, a member of the research team will review the patient and ask about any general health issues, missed doses, issues with the injection device and check the participant's pen diary and events diary for AEs. Full sharps bins will be returned to research teams for disposal and new bins provided. Research pharmacies will then issue new pens and collect in previously issued pens for basic accountability checks (unused pens or multiple missed doses).

Table 2 sets out the schedule of visits for participants allocated to the active treatment arm. Visits are scheduled for the final week of treatment to ensure that there are no gaps in supplies (i.e. participants issued with 16 weeks drug at baseline but attend site to collect their next supplies at 15 weeks).

TABLE 2	Baseline	15 weeks	31 weeks	52 weeks (12 month visit)	67 weeks	83 weeks	104 weeks (24 month visit)
No of pens issued	4	4	5	4	4	5	0
Pen diary data collected		X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	
Medications check		X	X	X	X	X	X
New prescription generated	X	X	X	X	X	X	X
Accountability data logged by pharmacy		X	X	X	X	X	X

FOLLOW UP VISIT AT 12 MONTHS (52 WEEKS)

The time window for this visit will be plus or minus 14 days from the date of randomisation. In a selected number of sites, a notification/thank you card will be sent to participants one month prior to the visit target date as part of a Study Within A Trial (SWAT).

- **Safety bloods:** A sample of venous blood will be collected and analysed locally by the laboratories at participating centres for serum creatinine, calculation of eGFR, , serum calcium, albumin and serum total alkaline phosphatase (ALP).

- **Research bloods:** Another sample of up to 10ml will be collected and allowed to clot. Serum will be separated on site and 2 x 1ml aliquots prepared. These will be stored frozen at -70°c or below at the study site and shipped on dry ice to the University of Edinburgh Bone Research Laboratory where they will be stored at -70°c or below until they are used for analysis of biochemical markers of bone turnover. The date and time of taking the blood samples will be noted on the CRF.

- **Clinical examination:** Recording of weight and height

- **HRQCT:** Patients who are attending centres with access to high resolution CT equipment will have the option of having a HRQCT scan of the wrist and tibia.

- **Participant Questionnaire Pack:** Questionnaires will be completed for SF36, HAQ, EQ5D, PSQI and the brief pain inventory (BPI).

- **Participant Diary, AE and medications check:** Data recorded on patient diaries (GP visits, hospital visits, hospital admissions and fractures) will be reviewed by research staff at the study sites and entered onto the study database.

FOLLOW UP VISIT AT 24 MONTHS (104 WEEKS)

The time window for this visit will be within 28 days from the date of randomisation in the standard care group and within 28 days of completing the 24 month course of TPTF in the active group. In a selected number of sites, a notification/thank you card will be sent to participants one month prior to the visit target date as part of a Study Within A Trial (SWAT).

- **Safety bloods:** A sample of venous blood will be collected and analysed locally by laboratories at participating centres for serum creatinine, calculation of eGFR, serum calcium, albumin, and serum total alkaline phosphatase (ALP).

- **Research bloods:** Another sample of up to 10ml will be collected and allowed to clot. Serum will be separated on site and 2 x 1ml aliquots prepared. These will be stored frozen at -70°c or below at the study site and shipped on dry ice to the University of Edinburgh Bone Research Laboratory where they will be stored at -70°c or below until they are used for analysis of biochemical markers of bone turnover. The date and time of taking the blood samples will be noted on the CRF.

- **Clinical examination:** Recording of weight and height.

- **DEXA:** Participants will undergo a bone mineral density scan using dual x-ray absorptiometry of the spine and hip by DEXA according to standard techniques, unless the local investigator feels that DEXA would not be feasible or informative (for example in patients with severe OI and multiple skeletal deformities or those with metalwork in situ that would preclude DEXA). This should be performed, as far as possible, on the same machine used for the baseline assessment.

- **HRQCT:** Patients who are attending centres with access to high resolution CT equipment will have the option of having a HRQCT scan of the wrist and tibia..

- **Participant Questionnaire Pack:** Questionnaires will be completed for SF36, HAQ, EQ5D, PSQI and the brief pain inventory (BPI).

- **Participant Diary, AE and medications check:** Data recorded on patient diaries (GP visits, hospital visits, hospital admissions and fractures) will be reviewed and entered onto the study database by research staff.

- **ZA infusion:** Participants allocated to the active treatment group (TPTD/ZA) will undergo an infusion of zoledronic acid 5mg intravenously following completion of TPTD therapy. This may either be performed on the same day at the 24 month visit or depending on logistical issues and patient convenience at a subsequent visit. Whenever possible the ZA infusion should be administered within 4 weeks of finishing TPTD.

- **Urine pregnancy test:** Women of childbearing potential (WOCBP), defined as women who are premenopausal who have not been sterilised and who have not been using a robust form of contraception (4.3.1) will require a negative urine pregnancy test prior to the infusion of ZA (or ZA alternative), .

END OF STUDY VISIT

The timing of the end of study visit will be dependent on accrual of fractures during the study since this is an event driven trial (section 9). It is expected that the end of study visit will on average, occur after participants have been on the study for 48 months but depending on the rate of fracture accrual it may occur at any time between 36 to 60 months after enrolment into the study. In a selected number of sites, a notification/thank you card will be sent to participants one month prior to the visit target date as part of a Study Within A Trial (SWAT).

- **Safety bloods:** A sample of venous blood will be collected and analysed locally by laboratories at participating centres for serum creatinine, calculation of eGFR, serum calcium, albumin and serum total alkaline phosphatase (ALP).

- **Research bloods**: Another sample of up to 10ml will be collected and allowed to clot. Serum will be separated on site and 2 x 1ml aliquots prepared. These will be stored frozen at -70°c or below at the study site and shipped on dry ice to the University of Edinburgh Bone Research Laboratory where they will be stored at -70°c or below until they are used for analysis of biochemical markers of bone turnover. The date and time of taking the blood samples will be noted on the CRF.

- **Clinical examination:** Recording of weight and height.

- **DEXA:** Participants will undergo a bone mineral density scan using dual x-ray absorptiometry of the spine and hip by DEXA according to standard techniques, unless the local investigator feels that DEXA would not be feasible or informative (for example in patients with severe OI and multiple skeletal deformities or those with metalwork in situ that would preclude DEXA). This should be performed, as far as possible, on the same machine used for the baseline and 24 month assessment.

- **Spine x-ray**: Lateral radiographs will be performed of the thoracic and lumbar spine to detect vertebral fractures.

- **HRQCT:** Patients who are attending centres with access to high resolution CT equipment will have the option of having a HRQCT scan of the wrist and tibia.

- **Participant Questionnaire Pack:** Questionnaires will be completed for SF36, HAQ, EQ5D, PSQI and the brief pain inventory (BPI).

- **Participant Diary, AE and medications check:** Data recorded on patient diaries (GP visits, hospital visits, hospital admissions and fractures) will be reviewed and entered onto the study database by research staff.

ASSESSMENTS FOR FRACTURE

Participants who think they have experienced a fracture during the trial will be advised to seek medical advice and if clinically indicated undergo x-ray or other imaging as appropriate to confirm or exclude the presence of a fracture. Participants will be advised to contact the local study centre with details of the hospital where the imaging had been performed. Sites are also asked to collect information on fractures including whether it resulted in hospitalisation and in any surgical or medical procedures (i.e. pinning) as per Section 10.1) Relevant x-ray images will be identified and retrieved by members of the study team. The de-identified images will be uploaded onto the study database or images copied onto CD and shipped to the co-ordinating centre for review.

The electronic images will be reviewed on an ongoing basis by an imaging expert based at the co-ordinating centre who is blinded to treatment allocation. The imaging expert will adjudicate if a fracture is present or not and will record within the database the site of the fracture.

Ascertainment of incident vertebral fractures will be achieved by comparing the appearances of spine radiographs at baseline and the end of study an imaging expert blinded to treatment allocation and recorded within the database. The images will be uploaded onto the study database after removing patient identifiable information, as described for the images performed for investigation of suspected clinical fractures.

TELEPHONE CONTACTS

Telephone contacts will be made every 6 months during the study (with a window of 14 days either side of the target date) to check if the participant is having any problems with the medication; to check on compliance; to gather information on adverse events and to gather information on fractures. Initial contact to prompt the participant can be by telephone, SMS or email depending on participant preference. If the participant has information to report (i.e. problems with medication; compliance, adverse events or fractures) then this should only be passed to the study team via telephone.

OPTIONAL CONTACTS

To promote retention in the trial participants will be offered the opportunity to sign up to receive regular updates about the progress of the trial and other communications such as Christmas cards and birthday cards.

8 DATA COLLECTION

It is anticipated that paper forms will be used for patient diaries and quality of life questionnaires which will be completed at the study visits or by sending the questionnaires to participants in advance. Standard tools will be used including SF36, HAQ, PSQI, EQ5D and the brief pain inventory (BPI). Electronic media may also be used to collect this data if suitable technology becomes available during the study.

The information collected will be transferred on an electronic CRF (eCRF) by research staff at study sites. The eCRF will be developed by data programmers at Edinburgh Clinical Trials Unit which will be the co-ordinating centre. The eCRF will include range checks to enhance data quality and tools to check for completeness of data. Other essential documents, including source data, consent forms, and regulatory documents, will be archived by or for the Investigator in an appropriate archive facility in line with current regulatory requirements and made available for monitoring, audit and regulatory inspection.

Completeness of data will be assessed during the study and local study centres alerted if there is a need to contact participants who have not completed questionnaires.

Data Management

9.1.1 Personal Data

The following personal data will be collected as part of the research:

- Health service or hospital patient identification number, name and email address (if volunteered for updates about the study), genetic data, physical and physiological information.

Personal data will be stored by the research team at the University of Edinburgh where it will be accessed from secure servers only by members of the direct research team.

Personal data will be stored for15 years alongside all the data collected as part of the study.

9.1.2 Transfer of Data

Data collected or generated by the study (including personal data) will analysed at the University of Edinburgh. We may also combine information from this trial with that of other completed and ongoing trials (a meta-analysis) to further explore the effects of these treatments. This may involve the release of anonymised data to collaborating partners in the EU.

9.1.3 Data Processor

The data processor is the Edinburgh Clinical Trials Unit, Usher Institute, University of Edinburgh.

9.1.4 Data Controller

The data controller is the University of Edinburgh and NHS Lothian who are the co-sponsors of this study.

10 STATISTICS AND DATA ANALYSIS

10.1 SAMPLE SIZE CALCULATION

The proposed sample size is 380 subjects (190 per treatment group).

The sample size has been arrived at based on the following assumptions.
(a) The proportion of patients experiencing a first fracture during each year of the trial will be 16%.
(b) The active treatment will reduce the proportion of patients who experience a first fracture by relative reduction of 25% as compared with standard care.
(c) The primary outcome will be time to first fracture analysed by the log-rank test taking into account baseline characteristics.
(d) The statistical power calculation is based on the cumulative risk difference at the 48 month time point.

Based on analysis of previous clinical trials and observational studies of adult OI patients (5-9) we expect the annual rate of participants experiencing a first fracture to be about 16% in the standard care group. If this assumption is correct and active treatment reduces the proportion of patients who experience a fracture by 25%, this equates to an absolute risk reduction over 4 years of 16% (from 64% to 48%) and a hazard ratio of 0.608.

With these assumptions, a sample size of 176 patients per group would be expected to result in 149 patients with new clinical fractures after an average of 48 months follow up. If the active treatment reduces the proportion of patients that experience a fracture by 25% we

would expect that in the standard care group there would be 90 patients with at least one fracture by 48 months as compared with 67 in the TPTD/ZA group.

The sample size will be inflated to 190 per group to account for missing data and the possibility that patients may be lost to follow up, giving a total sample size of 380. This assumes that up to 15% of patients may discontinue the intervention early or be lost to follow up, and that these drop-outs are evenly spread throughout follow-up. With these assumptions we have 85% power in analysis of the primary endpoint.

In the final analysis, statistical power will be further enhanced by stratifying the log-rank test for the prognostic factors being used in the minimisation procedure of the trial randomisation.

10.2 PROPOSED ANALYSES

A detailed statistical analysis plan (SAP) will be developed and finalised prior to the locking of the trial database in consultation with the trial steering committee. Here we outline the main principles to be followed. Throughout, a 5% two-sided significance level will be used. The intention to treat principle will be followed in the primary analysis. A per-protocol analysis will be performed as a sensitivity analysis: the per-protocol population will be identified and agreed by the trial steering committee (TSC) prior to database lock and analysis of the data.

There will be no formal interim analysis for early stopping due to efficacy or futility.

Primary outcome

The primary outcome will be the proportion of participants experiencing a clinical fracture validated by x-ray or other imaging. The main analysis of the primary outcome will summarise time to first fracture by treatment group using Kaplan-Meier survival curves, the groups being compared using the log-rank test stratified by the minimisation variables.

We will review accumulation of fractures during the study and review the situation at 48 months or when 149 patients have suffered a clinical fracture. This will be done by the blinded trial statistician and the DMC will then be asked to make a recommendation to the TSC on continuation (or termination) of the trial.

A secondary analysis will use binary logistic regression, with treatment group (active vs. standard care) and the minimisation variables (fracture in last 2 years, OI clinical subtype, gender, age, BMD group and bisphosphonate use at baseline or in 2 years prior to randomisation) as the independent variables. The effect of randomised treatment will be measured by the odds ratio (and 95% confidence interval) for TPTD/ZA vs. standard care. While every effort will be made to obtain complete follow-up data on all patients, it is recognised that in the OI population some study participants will be lost to follow-up. A sensitivity analysis in which missing data are imputed will be developed according to the principles outlined in (20), namely to develop an understanding for the reasons for loss to follow-up, define the primary set of assumptions about the missing data mechanism on this basis, conduct a statistically valid analysis under these assumptions and explore the robustness of the conclusions in further sensitivity analyses that capture departures from the primary missing data assumptions.

Secondary outcomes

The number of fractures (patient reported and imaging validated) will be analysed using a Poisson regression model, adjusting for the minimisation variables and, if required, including an overdispersion parameter.

Changes in BMD, bone pain, EQ5D, HAQ, SF36, PSQI will be analysed using analysis of covariance (ANCOVA). In each case the model will adjust for the baseline value and the minimisation variables.

Mechanistic Study

The mechanistic objective will be addressed in two stages. First, descriptive statistics of fracture rate will be summarised by treatment group for clinical subtype of OI, baseline BMD,

gender and molecular diagnosis. This will be used to inform a subsequent individual patient data meta-analysis combining the data from this trial and the TPTD and standard care groups from the trial led by co-applicant Professor Bente Langdahl which has started recruitment in Scandinavia (EudraCT 2011-002811-27) and by sourcing data from the trial previously reported by Orwoll in which TPTD was compared with placebo in patients with OI (9). These analyses will include a fixed effect for trial and will formally test, in a separate model for each baseline variable, for an interaction between the baseline variable and the effect of TPTD (versus standard care) on fracture rate. In further pooled analyses data from the standard care groups in both trials will be combined to estimate the association between each baseline variable and fracture risk in patients receiving standard care

11 ADVERSE EVENTS

The Investigator is responsible for the detection and documentation of events meeting the criteria and definitions detailed below.

Full details of contraindications and side effects that have been reported following administration of the IMP can be found in the relevant Summary of Product Characteristics (SmPC)

Participants will be instructed to contact their Investigator at any time after consenting to join the trial if any symptoms develop. All adverse events (AE) that occur after joining the trial must be reported in detail in the Case Report Form (CRF) or AE form. In the case of an AE, the Investigator should initiate the appropriate treatment according to their medical judgment. Participants with AEs present at the last visit must be followed up until resolution of the event.

11.1 DEFINITIONS

An **adverse event** (AE) is any untoward medical occurrence in a clinical trial participant which does not necessarily have a causal relationship with an investigational medicinal product (IMP).

An **adverse reaction** (AR) is any untoward and unintended response to an IMP which is related to any dose administered to that participant.

A **serious adverse event** (SAE), **serious adverse reaction** (SAR). Any AE or AR that at any dose:

- results in death of the clinical trial participant;
- is life threatening*;
- requires in-patient hospitalisation^ or prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity;
- consists of a congenital anomaly or birth defect;
- results in any other significant medical event not meeting the criteria above.

*Life-threatening in the definition of an SAE or SAR refers to an event where 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.

^Any hospitalisation that was planned prior to randomisation will not meet SAE criteria. Any hospitalisation that is planned post randomisation will meet the SAE criteria.

A suspected unexpected serious adverse reaction (SUSAR) is any AR that is classified as serious and is suspected to be caused by the IMP, that it is not consistent with the information about the IMP in the Summary of Product Characteristics (SmPC) or Investigators Brochure.

11.2 IDENTIFYING AEs AND SAEs

All AEs and SAEs will be recorded from the time a participant signs the consent form to take part in the study until the final study visit. Participants with adverse events will be followed up until they have resolved.

Participants will be asked about the occurrence of AEs/SAEs at every visit during the study. Open-ended and non-leading verbal questioning of the participant will be used to enquire about AE/SAE occurrence. Participants will also be asked if they have been admitted to hospital, had any accidents, used any new medicines or changed concomitant medication regimens. If there is any doubt as to whether a clinical observation is an AE, the event will be recorded.

AEs and SAEs may also be identified via information from support departments such as abnormal results occurring as the result of routine laboratory safety testing performed during the study.

11.3 RECORDING AEs AND SAEs

When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the event. The Investigator will then record all relevant information in the CRF and on the SAE form (if the AE meets the criteria of serious).

Information to be collected includes dose, type of event, onset date, Investigator assessment of severity and causality, date of resolution as well as treatment required, investigations needed and outcome.

11.4 ASSESSMENT OF AEs AND SAEs

Seriousness, causality, severity and expectedness will be assessed by the Principal Investigator. For randomised double-blind studies, AEs will be assessed as though the participant is taking active IMP. Cases that are considered serious, possibly, probably or definitely related to IMP and unexpected (i.e. SUSARs) will be unblinded.

The Investigator is responsible for assessing each AE but this may be delegated to other members of the study team.

The Chief Investigator (CI) may not downgrade an event that has been assessed by an Investigator as an SAE or SUSAR, but can upgrade an AE to an SAE, SAR or SUSAR if appropriate.

11.4.1 Assessment of Seriousness

The Investigator will make an assessment of seriousness as defined in Section 10.1.

11.4.2 Assessment of Causality

The Investigator will make an assessment of whether the AE/SAE is likely to be related to the IMP according to the definitions below.

- Unrelated: where an event is not considered to be related to the IMP.

Possibly Related: The nature of the event, the underlying medical condition, concomitant medication or temporal relationship make it possible that the AE has a causal relationship to the study drug. The assessment of causality will be made against the reference safety information (RSI) found in the representative Summary of Product Characteristics. Investigators may use different brands of the drugs than those listed in the representative SPC but should continue to make assessments of causality against the RSI in the representative SPC.

Where non Investigational Medicinal Products (NIMPs) e.g. rescue/escape drugs are given: if the AE is considered to be related to an interaction between the IMP and the NIMP, or where the AE might be linked to either the IMP or the NIMP but cannot be clearly attributed to either one of these, the event will be considered as an AR. Alternative causes such as natural history of the underlying disease, other risk factors and the temporal relationship of the event to the treatment should be considered and investigated. The blind should not be broken for the purpose of making this assessment.

11.4.3 Assessment of Expectedness

If an event is judged to be an AR, the evaluation of expectedness will be made based on knowledge of the reaction and the relevant product information documented in the SmPC.

The event may be classed as either:

Expected: the AR is consistent with known adverse events associated with the IMP listed in the SmPC.

Unexpected: the AR is not consistent with known adverse events associated with the IMP as listed in the SmPC.

11.4.4 Assessment of Severity

The Investigator will make an assessment of severity for each AE/SAE and record this on the CRF or SAE form according to one of the following categories:

Mild: an event that is easily tolerated by the participant, causing minimal discomfort and not interfering with every day activities.

Moderate: an event that is sufficiently discomforting to interfere with normal everyday activities.

Severe: an event that prevents normal everyday activities.

Note: the term 'severe', used to describe the intensity, should not be confused with 'serious' which is a regulatory definition based on participant/event outcome or action criteria. For example, a headache may be severe but not serious, while a minor stroke is serious but may not be severe.

11.5 REPORTING OF SAEs/SARs/SUSARs

ADVERSE EVENTS THAT DO NOT REQUIRE TO BE REPORTED TO THE SPONSOR (EVEN IF MEETING SERIOUSNESS CRITERIA)

Fractures are an expected occurrence in OI and are the trial endpoint. Incident fractures that occur during the trial will be recorded (using the New Fracture Report) but not reported to the Sponsor. If an incident fracture requires hospitalisation or a medical or surgical procedure (i.e. pinning) then this information should be added to the fracture report and it will **not** be reported as a Serious Adverse Event.

Once the Investigator becomes aware that an SAE has occurred in a study participant, the information will be reported to the ACCORD Research Governance & QA Office **immediately or within 24 hours**. If the Investigator does not have all information regarding an SAE, they should not wait for this additional information before notifying ACCORD. The SAE report form can be updated when the additional information is received.

The SAE report will provide an assessment of causality and expectedness at the time of the initial report to ACCORD according to Sections 10.4.2, Assessment of Causality and 10.4.3, Assessment of Expectedness.

The SAE form will be transmitted by fax to ACCORD on **+44 (0)131 242 9447** or may be transmitted by hand to the office or submitted via email to Safety.Accord@ed.ac.uk. Only forms in a pdf format will be accepted by ACCORD via email.

ACCORD will onward report SARs/SUSARs to Eli Lilly within 24 hours of notification via email to UK_Team_Gbmail-GPS@lilly.com

Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the investigator and request the missing information.

All reports faxed to ACCORD and any follow up information will be retained by the Investigator in the Investigator Site File (ISF).

11.6 REGULATORY REPORTING REQUIREMENTS

The ACCORD Research Governance & QA Office is responsible for pharmacovigilance reporting on behalf of the co-sponsors (Edinburgh University and NHS Lothian).

The ACCORD Research Governance & QA Office has a legal responsibility to notify the regulatory competent authority and relevant ethics committee (Research Ethics Committee (REC) that approved the trial). Fatal or life threatening SUSARs will be reported no later than 7 calendar days and all other SUSARs will be reported no later than 15 calendar days after ACCORD is first aware of the reaction.

ACCORD will inform Investigators at participating sites of all SUSARs and any other arising safety information.

An Annual Safety Report/Development Safety Update Report (DSUR) will be submitted, by ACCORD, to the regulatory authorities and RECs listing all SARs and SUSARs. ACCORD will also submit a copy of the DSUR to Eli Lilly via email to UK_Team_Gbmail-GPS@lilly.com

11.7 FOLLOW UP PROCEDURES

After initially recording an AE or recording and reporting an SAE, the Investigator should make every effort to follow each event until a final outcome can be recorded or reported as necessary. Follow up information on an SAE will be reported to the ACCORD office.

If, after follow up, resolution of an event cannot be established, an explanation should be recorded on the CRF or AE log or additional information section of SAE form.

12 PREGNANCY

Pregnancy tests will be performed at the baseline visit in women of childbearing potential. Additionally, a pregnancy test will be performed at 24 months prior to the infusion of ZA. Further pregnancy tests may be performed at any time at the discretion of the local investigator if they have reason to believe that a female participant has become pregnant despite taking adequate contraceptive measures.

During the study pregnancy information will be collected for any female participants or female partners of male participants who become pregnant while participating in the study. The Investigator will record the information on a Pregnancy Notification Form and submit this to the ACCORD office within 14 days of being made aware of the pregnancy. Pregnancy will not be considered an AE or SAE. If a woman that is being currently treated with bisphosphonates or TPTD becomes pregnant during the study, these treatments will be stopped for the duration of the pregnancy. No specific action is required with regard to pregnancy in female partners of males that are being treated with TPTD or bisphosphonates during the study.

13 TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

13.1 TRIAL MANAGEMENT GROUP

The trial will be coordinated by a Project Management Group, consisting of the grant holders (Chief Investigator and Principal Investigator in Edinburgh), A Trial Manager and the trial statistician

The Trial Manager will oversee the study and will be accountable to the Chief Investigator. The Trial Manager will be responsible for checking the CRFs for completeness, plausibility and consistency. Any queries will be resolved by the Investigator or delegated member of the trial team.

A Delegation Log will be prepared for each site, detailing the responsibilities of each member of staff working on the trial.

13.2 TRIAL STEERING COMMITTEE

A Trial Steering Committee (TSC) will be established to oversee the conduct and progress of the trial. The TSC will consist of an independent chair with clinical experience in rheumatology or bone disease, an independent statistician, an independent clinician with experience in rheumatology or bone disease, an independent individual representing the stakeholder group of patients with OI, a patient representative; a representative from the sponsor, the principal investigator and one of the grant holders. The terms of reference and operation of the TSC will conform to the research governance guidelines in operation at the EME.

http://www.nets.nihr.ac.uk/__data/assets/pdf_file/0014/165110/NETSCC_TSC_SSC-Guidance_April-2016.pdf

The names and contact details of the TSC will be detailed in a separate document.

13.3 DATA MONITORING COMMITTEE

An independent Data Monitoring Committee (DMC) will be established to oversee the safety of participants in the trial. The DMC will consist of an independent chair with clinical experience in rheumatology or bone disease, an independent statistician, and a second independent clinician with experience in rheumatology or bone disease.

The terms of reference operation of the DMC will conform to the research governance guidelines in operation at the EME.

http://www.nets.nihr.ac.uk/__data/assets/pdf_file/0014/165110/NETSCC_TSC_SSC-Guidance_April-2016.pdf

The names and contact details of the DMC will be detailed in a separate document.

13.4 INSPECTION OF RECORDS

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

13.5 RISK ASSESSMENT

An independent risk assessment will be performed by an ACCORD Clinical Trials Monitor to determine if monitoring is required and if so, at what level. An independent risk assessment will also be carried out by the ACCORD Quality Assurance Group to determine if an audit should be performed before/during/after the study and if so, at what locations and at what frequency.

13.6 STUDY MONITORING AND AUDIT

An ACCORD Clinical Trials Monitor or an appointed monitor will visit the Investigator site prior to the start of the study and during the course of the study if required, in accordance with the monitoring plan if required. Risk assessment will determine if audit, by the ACCORD QA group, is required. Details will be captured in an audit plan. Audit of Investigator sites, study management activities and study collaborative units, facilities and 3rd parties may be performed.

14 GOOD CLINICAL PRACTICE

14.1 ETHICAL CONDUCT

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP).

A favorable ethical opinion will be obtained from the appropriate REC and local R&D approval will be obtained prior to commencement of the study.

14.2 REGULATORY COMPLIANCE

The study will not commence until a Clinical Trial Authorisation (CTA) is obtained from the appropriate Regulatory Authority. The protocol and study conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended.

14.3 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff.

14.3.1 Informed Consent

The Investigator is responsible for ensuring informed consent is obtained before any protocol specific procedures are carried out. The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

Participants must receive adequate oral and written information – appropriate Participant Information and Informed Consent Forms will be provided. The oral explanation to the participant will be performed by the Investigator or qualified delegated person, and must cover all the elements specified in the Participant Information Sheet and Consent Form.

The participant must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant must be given sufficient time to consider the information provided. It should be emphasised that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The participant will be informed and agree to their medical records being inspected by regulatory authorities and representatives of the sponsor(s) but understand that their name will not be disclosed outside the hospital.

The Investigator or delegated member of the trial team and the participant will sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The participant will receive a copy of this document and a copy filed in the Investigator Site File (ISF) and participant's medical notes.

14.3.2 Study Site Staff

The Investigator must be familiar with the IMP, protocol and the study requirements. It is the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the IMP, protocol and their trial related duties.

14.3.3 Data Recording

The Principle Investigator is responsible for the quality of the data recorded in the CRF at each Investigator Site. The source data plan identifies which source data correspond to CRF data and states which data are recorded directly into the CRF.

14.3.4 Investigator Documentation

Prior to beginning the study, each Investigator will be asked to provide particular essential documents to the ACCORD Research Governance & QA Office, including but not limited to:

- An original signed Investigator's Declaration (as part of the Clinical Trial Agreement documents);
- Curriculum vitae (CV) signed and dated by the Investigator indicating that it is accurate and current.

The ACCORD Research Governance & QA Office will ensure all other documents required by ICH GCP are retained in a Trial Master File (TMF), where required, and that appropriate documentation is available in local ISFs.

14.3.5 GCP Training

All study staff must hold evidence of appropriate GCP training.

The exception to this will be radiology staff performing DEXA scanning and HR-pQCT. These personnel will document training on the study-specific scanning protocol, GxP guidance and the scanning database.

14.3.6 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant. The Investigator and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

14.3.7 Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the appropriate data protection legislation (including the General Data Protection Regulation and Data Protection Act). Access to collated participant data will be restricted to those clinicians treating the participants, representatives of the sponsor(s) and representatives of regulatory authorities.

Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data that could allow identification of individual participants.

15 STUDY CONDUCT RESPONSIBILITIES

15.1 PROTOCOL AMENDMENTS

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of a urgent safety measure, must be reviewed and approved by the Chief Investigator.

Amendments to the protocol must be submitted in writing to the appropriate REC, Regulatory Authority and local R&D for approval and to Eli Lilly for information prior to participants being enrolled into an amended protocol.. Amended protocols and approvals will also be sent to Eli Lilly via email to UK_Team_Gbmail-GPS@lilly.com

15.2 PROTOCOL VIOLATIONS AND DEVIATIONS

Prospective protocol deviations, i.e. protocol waivers, will not be approved by the sponsors and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this should be submitted to the REC, Regulatory Authority and local R&D for review and approval if appropriate.

Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the sponsors every 3 months. Each protocol violation will be reported to the sponsor within three days of becoming aware of the violation.

15.3 SERIOUS BREACH REQUIREMENTS

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 trial; or

(b) the scientific value of the trial.

If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the co-sponsors (accord.seriousbreach@ed.ac.uk) must be notified within 24 hours. It is the responsibility of the co-sponsors to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and report to regulatory authorities and research ethics committees as necessary.

15.4 STUDY RECORD RETENTION

All study documentation will be kept for a minimum of 5 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

15.5 END OF STUDY

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

The Investigators and/or the trial steering committee and/or the co-sponsor(s) have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC, Regulatory Authority, R&D Office(s) and co-sponsors within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow-up is arranged for all participants involved. End of study notification will be reported to the co-sponsors via email to researchgovernance@ed.ac.uk.

In accordance with ACCORD SOP CR011, a Clinical Study Report (CSR) will be provided to the Sponsor (QA@accord.scot) and REC within 1 year of the end of the study. A study report and manuscript (including summary results for the primary and secondary objectives) will be submitted to Eli Lilly within 90 days of completion of the study.

Upon completion of the study, the investigator will upload clinical trial results onto the EudraCT database on behalf of the Sponsor.

The Investigator will submit a short confirmatory email to the MHRA (CT.Submission@mhra.gsi.gov.uk) and HPRA (clinicaltrials@hpra.ie) once the result-related information has been uploaded to EudraCT, with 'End of trial: result-related information: EudraCT 2016-003228-22' as the subject line. The Sponsor(s) will be copied in this email (QA@accord.scot). It should be noted that an acknowledgment email or letter will not be supplied by the MHRA.

15.6 CONTINUATION OF DRUG FOLLOWING THE END OF STUDY

Individual sites will assess participants according to standard clinical practice to determine what therapy (if any) should be continued following cessation of the study. The continuation of study therapy following the end of the study rests with the judgement of the treating physician.

15.7 INSURANCE AND INDEMNITY

The co-sponsors are responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the co-sponsors' responsibilities:

- The Protocol has been designed by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.
- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The co-sponsors require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities.
- Sites which are part of the United Kingdom's Nation Health Service will have the benefit of NHS Indemnity.
- Sites out with the United Kingdom will be responsible for arranging their own indemnity or insurance for their participation in the study, as well as for compliance with local law applicable to their participation in the study.
- The manufacturer supplying IMP has accepted limited liability related to the manufacturing and original packaging of the study drug and to the losses, damages, claims or liabilities incurred by study participants based on known or unknown Adverse Events which arise out of the manufacturing and original packaging of the study drug, but not where there is any modification to the study drug (including without limitation re-packaging and blinding).

16 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

16.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared in accordance with ICH guidelines.

16.2 PUBLICATION

The clinical study report will be used as the basis for publications and presentations of the results of the trial as abstracts scientific meetings. Authorship of abstracts and publications arising from the trial will include the grant holders and investigators at participating sites subject to the individuals fulfilling the criteria for authorship as recommended by the International Committee of Medical Journal Editors. A separate document outlining the publication policy and authorship for publications arising from the study will be prepared and implemented subject to the approval of the TSC.

Summaries of results will also be made available to investigators for dissemination within their clinics where appropriate and according to their discretion and to members of the brittle bone society and general public through the BBS and RUDY websites

16.3 PEER REVIEW

The study concept and design has been reviewed by the EME as part of the funding application process.

Investigators at each site, the Trial Steering Committee, Ethical Review Boards, MHRA, and local R&D departments will review the protocol as part of the study approval process.

The results of the study will be disseminated by peer review publication and presentation at national and international meetings.

17 REFERENCES

(1) Lindahl K, Astrom E, Rubin CJ, Grigelioniene G, Malmgren B, Ljunggren O et al. Genetic epidemiology, prevalence, and genotype-phenotype correlations in the Swedish population with osteogenesis imperfecta. Eur J Hum Genet ;23:1112.

(2) Cundy T. Recent advances in osteogenesis imperfecta. Calcif Tissue Int ;90:439-49.

(3) Paterson CR, McAllion S, Stellman JL. Osteogenesis imperfecta after the menopause. N Engl J Med ;310:1694-6.

(4) Wekre LL, Eriksen EF, Falch JA. Bone mass, bone markers and prevalence of fractures in adults with osteogenesis imperfecta. Arch Osteoporos ;6:31-8.

(5) Gatti D, Rossini M, Viapiana O, Povino MR, Liuzza S, Fracassi E et al. Teriparatide treatment in adult patients with osteogenesis imperfecta type I. Calcif Tissue Int ;93:448-52.

(6) Adami S, Gatti D, Colapietro F, Fracassi E, Braga V, Rossini M et al. Intravenous neridronate in adults with osteogenesis imperfecta. J Bone Miner Res ;18:126-30.

(7) Chevrel G, Schott AM, Fontanges E, Charrin JE, Lina-Granade G, Duboeuf F et al. Effects of oral alendronate on BMD in adult patients with osteogenesis imperfecta: a 3-year randomized placebo-controlled trial. J Bone Miner Res ;21:300-6.

(8) Bradbury LA, Barlow S, Geoghegan F, Hannon RA, Stuckey SL, Wass JA et al. Risedronate in adults with osteogenesis imperfecta type I: increased bone mineral density and decreased bone turnover, but high fracture rate persists. Osteoporos Int ;23:285-94.

(9) Orwoll ES, Shapiro J, Veith S, Wang Y, Lapidus J, Vanek C et al. Evaluation of teriparatide treatment in adults with osteogenesis imperfecta. J Clin Invest ;124:491-8.

(10) Paterson CR, Mole PA. Bone density in osteogenesis imperfecta may well be normal. Postgrad Med J ;70:104-7.

(11) Phillipi CA, Remmington T, Steiner RD. Bisphosphonate therapy for osteogenesis imperfecta. Cochrane Database Syst Rev ;CD005088.

(12) Dwan K, Phillipi CA, Steiner RD, Basel D. Bisphosphonate therapy for osteogenesis imperfecta. Cochrane Database Syst Rev ;7:CD005088.

(13) Hald JD, Evangelou E, Langdahl BL, Ralston SH. Bisphosphonates for the prevention of fractures in osteogenesis imperfecta: meta-analysis of placebo-controlled trials. J Bone Miner Res ;30:929-33.

(14) Boivin GY, Chavassieux PM, Santora AC, Yates J, Meunier PJ. Alendronate increases bone strength by increasing the mean degree of mineralization of bone tissue in osteoporotic women. Bone ;27:687-94.

(15) Brizola E, Shapiro JR. Bisphosphonate Treatment of Children and Adults with Osteogenesis Imperfecta: Unanswered Questions. Calcif Tissue Int ;97:101-3.

(16) Reid IR, Lyles K, Su G, Brown J, Walsh J, Del Pino-Montes J et al. A single infusion of zoledronic acid produces sustained remissions in Paget's disease - data to 6.5 years. J Bone Miner Res ;26:2270.

(17) Grey A, Bolland M, Wattie D, Horne A, Gamble G, Reid IR. Prolonged antiresorptive activity of zoledronate: a randomized, controlled trial. J Bone Miner Res ;25:2251-5.

(18) Obermayer-Pietsch BM, Marin F, McCloskey EV, Hadji P, Farrerons J, Boonen S et al. Effects of two years of daily teriparatide treatment on BMD in postmenopausal women with severe osteoporosis with and without prior antiresorptive treatment. J Bone Miner Res ;23:1591-600.

(19) Langston AL, Campbell MK, Fraser WD, MacLennan GS, Selby PL, Ralston SH. Randomised Trial of Intensive Bisphosphonate Treatment Versus Symptomatic Management in Paget's Disease of Bone. J Bone Miner Res ;25:20-31.

(20) Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron.* 1976; 16:31-41.

(21) Little RJ, D'Agostino R, Cohen ML, Dickersin K, Emerson SS, Farrar JT et al. The prevention and treatment of missing data in clinical trials. N Engl J Med ;367:1355-60.

APPENDIX 1

Contributors to protocol

The study was conceived and designed by Prof Stuart H Ralston and Prof Bente Langdahl. Professor Chris Weir provided statistical expertise and contributed to the study design. Dr Kassim Javaid, Jenny Walsh, Wayne Lam and Ms Patricia Osborne contributed to refinement of the protocol. All investigators reviewed and approved the protocol.

Role of Sponsor and Funders

The sponsors and funders had no role in the design of the study or its execution, analysis, interpretation of the data or decision to submit results for publication

APPENDIX 2

Standard operating procedures

The study will be performed according to the relevant standard operating procedures in operation published by the ACCORD office.

http://www.accord.scot/research-access/resources-researchers/sop

Note: When study sites are initiated, hard copies of the relevant SOP on serious breaches of GCP (SOP CR003) and on identifying and reporting AEs, SAEs (SOP CR005) and on Deviations and Violations (SOP CR010) will be placed in the investigator site file.