The BLAST OFF (Bisphosphonate aLternAtive regimenS for the prevenTion of Osteoporotic Fragility Fractures) Study

The BLAST OFF Study

IRAS	271732
REC	19/NW/0714
Study ID	19HC008
Funder	NIHR (HTA)

Protocol Version 1.1
11/12/2019

This protocol has been designed to ensure regard for the HRA guidance

FULL / LONG TITLE OF THE STUDY

The BLAST OFF (Bisphosphonate aLternAtive regimenS for the prevenTion of Osteoporotic Fragility Fractures) Study

SHORT STUDY TITLE / ACRONYM

The BLAST OFF Study

PROTOCOL VERSION NUMBER AND DATE

V1.1 11/12/2019

RESEARCH REFERENCE NUMBERS

IRAS Number:	271732
SPONSORS Number:	19HC008
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OTHER RESEARCH REFERENCE NUMBERS

SPONSOR

Nottingham University Hospitals NHS Trust
Nottingham Health Science Partners
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Telephone: 0115 9709049
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SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature: Date:
.....
......./...../.....

Name (please print):
.....

Position:
.....

Chief Investigator:

Signature: Date:
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......./...../.....

Name: (please print):
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Joint-sponsor(s)/co-sponsor(s)	N/A
Funder(s)	NIHR Health Services and Delivery Research (HS & DR)
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STUDY SUMMARY

Study Title	The BLAST OFF (Bisphosphonate aLternAtive regimenS for the prevenTion of Osteoporotic Fragility Fractures) Study
Internal ref. no. (or short title)	The BLAST OFF Study
Study Design	Data collection will involve qualitative non-probabilistic sampling, using representative and purposive sampling. Scoping review, systematic review and prioritisation exercise.
Study Participants	Stakeholders in the delivery and receipt of bisphosphonate regimes for the prevention of osteoporotic fragility fractures. Details in sample size below.
Planned Size of Sample (if applicable)	70 in total. Of which to include approximately; - 45 patients (20 sampled from primary care, 25 from secondary care) - 10 General Practitioners - 10 clinical professionals (doctors, nurses and researchers) working in secondary care - 5 additional clinical professionals working in sites with novel treatment regimens
Follow up duration (if applicable)	N/A
Planned Study Period	November 2019 – November 2021
Research Question/Aim(s)	To elicit patient and clinician experiences of using different bisphosphonate regimens, and understand patient, clinician and other stakeholders (including academics' and commissioners') preferences for alternative bisphosphonates regimens compared to Alendronate.

List of Acronyms

BLAST OFF Bisphosphonate aLternAtive regimenS for the prevenTion of Osteoporotic Fragility Fractures

CCG Clinical Commissioning Group

CI Chief Investigator

CRN Clinical Research Network

FLS Fracture Liaison Service

GCP Good Clinical Practice

GP General Practitioner

HTA Health Technology Assessment

ICH International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

NHS National Health Service

NHS R&D National Health Service Research and Development

NICE National Institute of Health and Care Excellence

NIHR (HS&DR) National Institute for Health Research (Health Services and Delivery Research)

NotROS Nottingham Royal Osteoporosis Society

NUBS Nottingham University Business School

NUH Nottingham University Hospitals

PCR Primary Care Rheumatology

PICO Problem Intervention Comparison Outcome

PPI Patient and Public Involvement

REC Research Ethics Committee

ROS Royal Osteoporosis Society

SMG Study Management Group

SOP Standard Operating Procedures

SSG Study Steering Group

UoN University of Nottingham

FUNDING

FUNDER(S) (Names and contact details of ALL organisations providing funding and/or support in kind for this study)	**FINANCIAL AND NON FINANCIALSUPPORT GIVEN**
NIHR (Health Services and Delivery Research) NIHR Evaluation, Trials and Studies Co-ordinating Centre University of Southampton Alpha House, Enterprise Road SO16 7NS Phone: 023 8059 4304 Email: hsdrinfo@nihr.ac.uk	Research Funder £530,627.34

This study is funded by the National Institute for Health Research (NIHR) [Health Technology Assessment Programme, project reference NIHR 127550]. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

ROLE OF STUDY SPONSOR AND FUNDER

Nottingham University Hospitals NHS Trust is the research sponsor for this study. Its role includes:

- Assuming overall responsibility for the conduct of the study.
- Inspecting and auditing the study under their remit to ensure adherence to Good Clinical Practice.
- The right to discontinue the study at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The sponsor shall take advice as appropriate in making this decision.
- Together with the designated NHS National Research Ethics Services and NHS R&D office(s), approve amendments to the study protocol and documents.
- Deal with breaches of Good Clinical Practice and adverse events related to the study.
- Provide usual NHS indemnity as sponsor to its staff and research participants.

The study sponsor will monitor the study conduct against nationally agreed standards. The study sponsor and study funder will have no role in the design, data analysis, interpretation, manuscript writing and dissemination of the results. The sponsor and funders do not control the final decision regarding any aspects of this study.

For further information regarding sponsorship, please contact:

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Email: researchsponsor@nuh.nhs.uk

ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITTEES/GROUPS & INDIVIDUALS

Study Steering Group

The Study Steering Group (SSG) will meet three times over the course of the project (on commencement, midpoint and end of data collection). The steering group will provide independent oversight and direction on all aspects of the study, with comprehensive update reports provided by the Study Management Group (SMG). The steering group holds relevant subject, methodological and patient expertise/experience. The steering group will include:

Dr Nicola Peel (Chair), Consultant Physician and Honorary Senior Clinical Lecturer in Metabolic Bone Medicine, Sheffield Teaching Hospitals NHS Trust
Karen Barker, Professor of Physiotherapy, Nuffield Department of Orthopaedics Rheumatology and Musculoskeletal Sciences (NDORMS), University of Oxford
Dr Alexander Thompson, Research Fellow in Health Economics, The University of Manchester
Ms Linsey Wallis, Lay Member Representative
Dr Pauline Hyman-Taylor, Sponsor Representative, Nottingham University Hospitals NHS Trust (or delegated member of the sponsor team)

Study Management Group

The Study Management Group (SMG) will consist of the Chief Investigator (CI) and all co-investigators (see below for protocol contributors), plus the Research Fellows recruited for the study. The SMG will be responsible for day to day management of the study and ensuring high quality delivery of the study according to the agreed timelines. This will include early identification of potential problems and implementing solutions to overcome them. With particular responsibility for the collection of data:

Professor Opinder Sahota (Nottingham University Hospitals) as Chief Investigator takes overall responsibility for the management and completion of the study.

The qualitative research will be led by Simon Bishop (Associate Professor, Nottingham University Business School, University of Nottingham). SB will take line management responsibility for the Research Fellow who will be recruited and employed by Nottingham University Business School. SB will conduct and manage data collection and analysis alongside the Research Fellow.

Patient & Public Involvement Group

Patient and public involvement (PPI) groups will be closely involved in the management of the research. We are working closely with the Royal Osteoporosis Society (ROS) UK - the only UK wide charity dedicated to improving the care of people with osteoporosis - and the Nottingham ROS (NotROS) Support Group. Following the commissioned call, we have undertaken 2 focus groups, one with the ROS (n=3) and one with the NotROS (n=7), who have influenced the design of this study (suggestion of interviews with service users and service commissioners), choice of study outcomes, and will be involved throughout the study. The ROS and 2 members of the NotROS have agreed to be co-applicants, all of whom have previous research experience.

Our PPI groups will be closely involved in the further management of the research, developing participant information resources, contributing to the reporting of the research and dissemination of research findings. AB and MH are named co-applicants for the NotROS group and will work with the SMG throughout the project. Their experiences as patients suffering with osteoporosis and access to services will be invaluable in better understanding the patient journey. AB and MH will also draw on

the wider views of the NotROS 250 patient membership, as required. This may include asking other members to become involved and acting as a further platform for PPI. PPI members from the NotROS group will undergo the standard Nottingham University Hospitals (NUH) PPI training programme, further supported by the NUH PPI team.

Protocol Contributors

This protocol has been developed by the study Chief Investigator and co-investigators. The PPI group has been consulted in the development of the protocol, including focus groups with the ROS, with details above. Co-investigators are:

Professor Jo Leonardi-Bee (JLB), Professor and Head of the Systematic Review Group, University of Nottingham

Ms Sarah Davis (SD), Senior Lecturer in Health Economics, University of Sheffield

Dr Simon Bishop (SB), Associate Professor of Organisational Behaviours, University of Nottingham

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Mrs Ann Baily (AB), Lay Member

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Mrs Alison Doyle (AD), Acting Clinical Director, Royal Osteoporosis Society

KEY WORDS:

Osteoporotic fragility fractures

Bisphosphonate treatment regimens

Systematic review

Qualitative interviews

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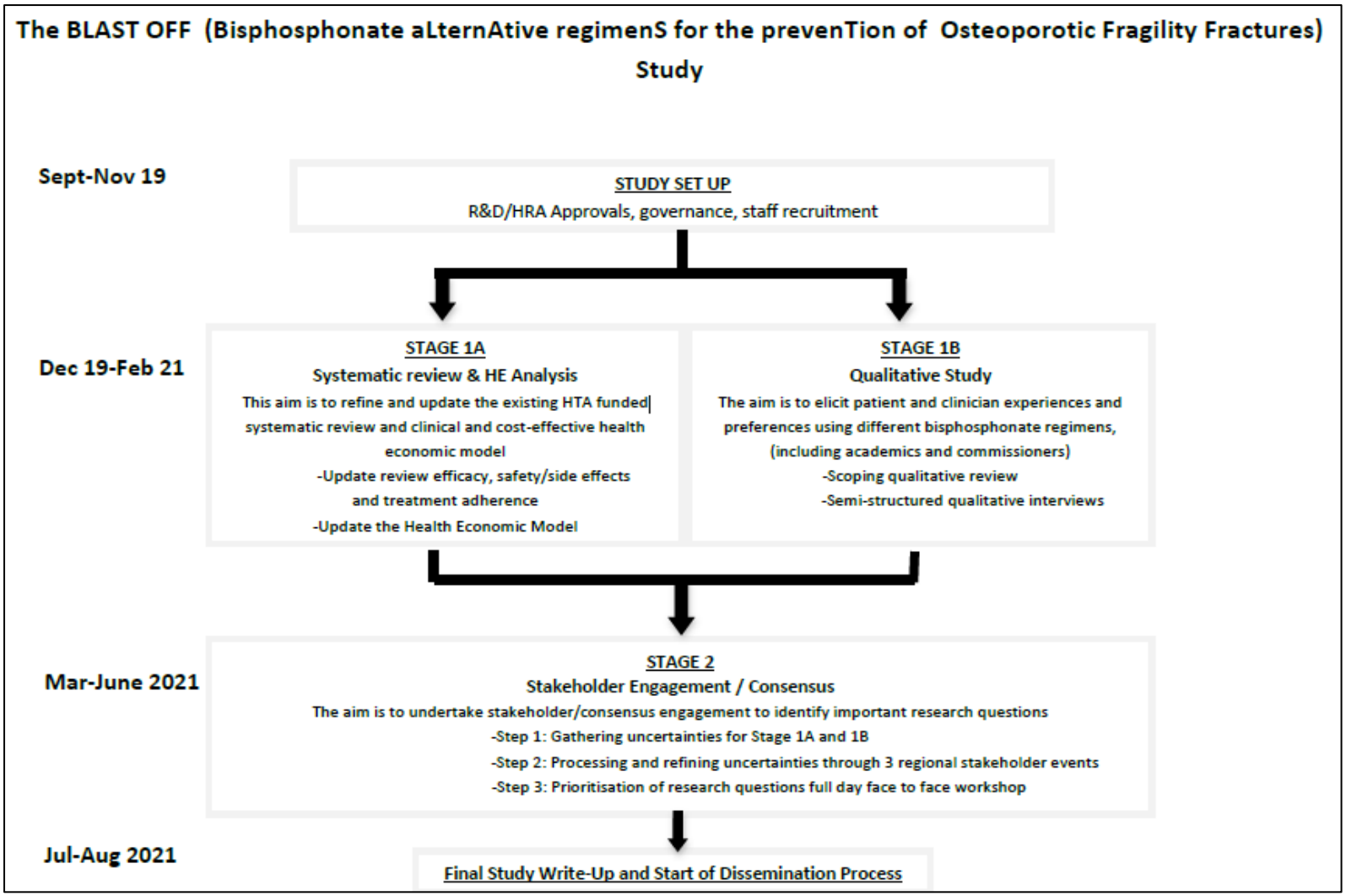
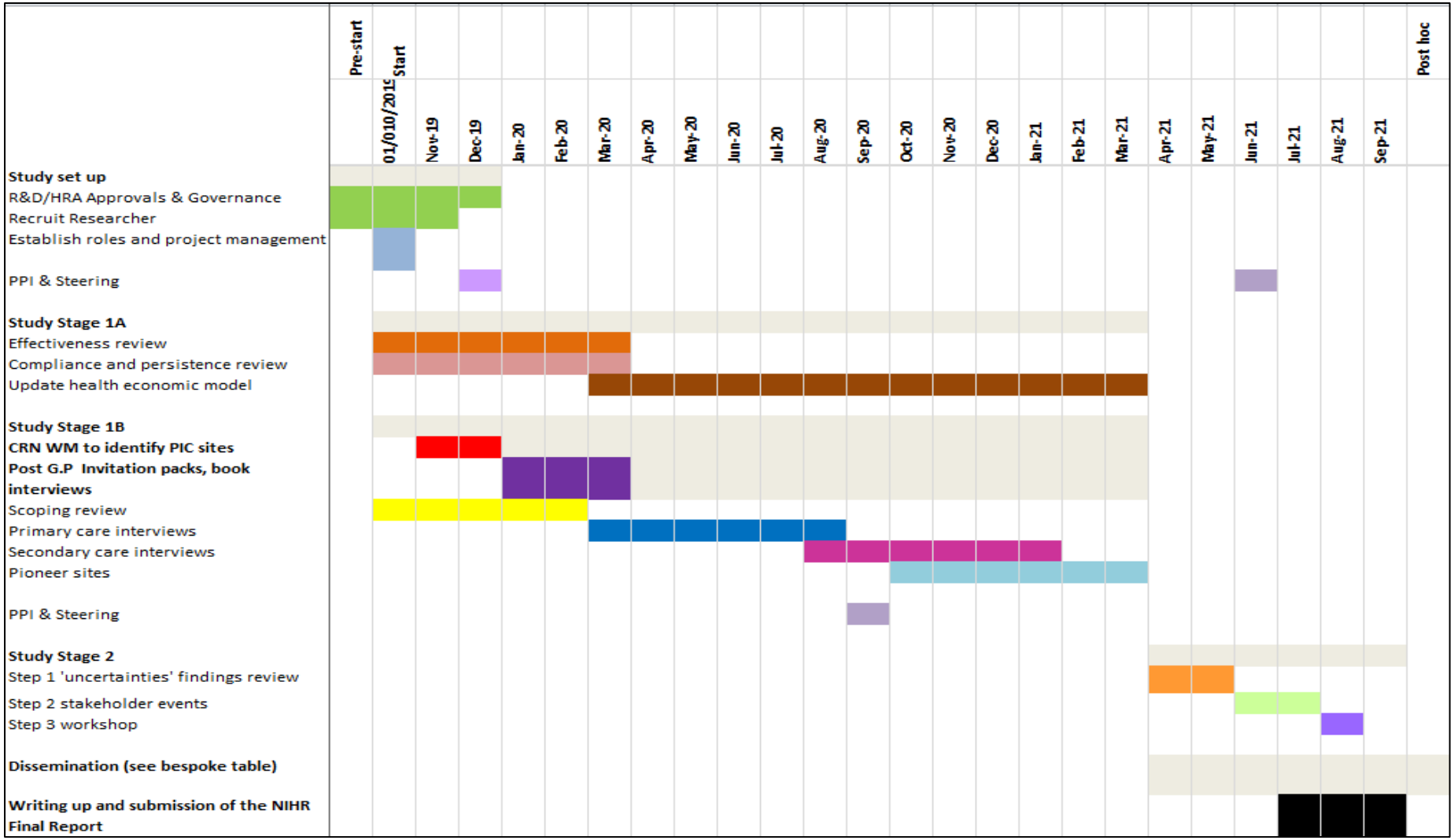
STUDY FLOW CHART



STUDY GANTT CHART



RECRUITMENT FLOW DIAGRAMS

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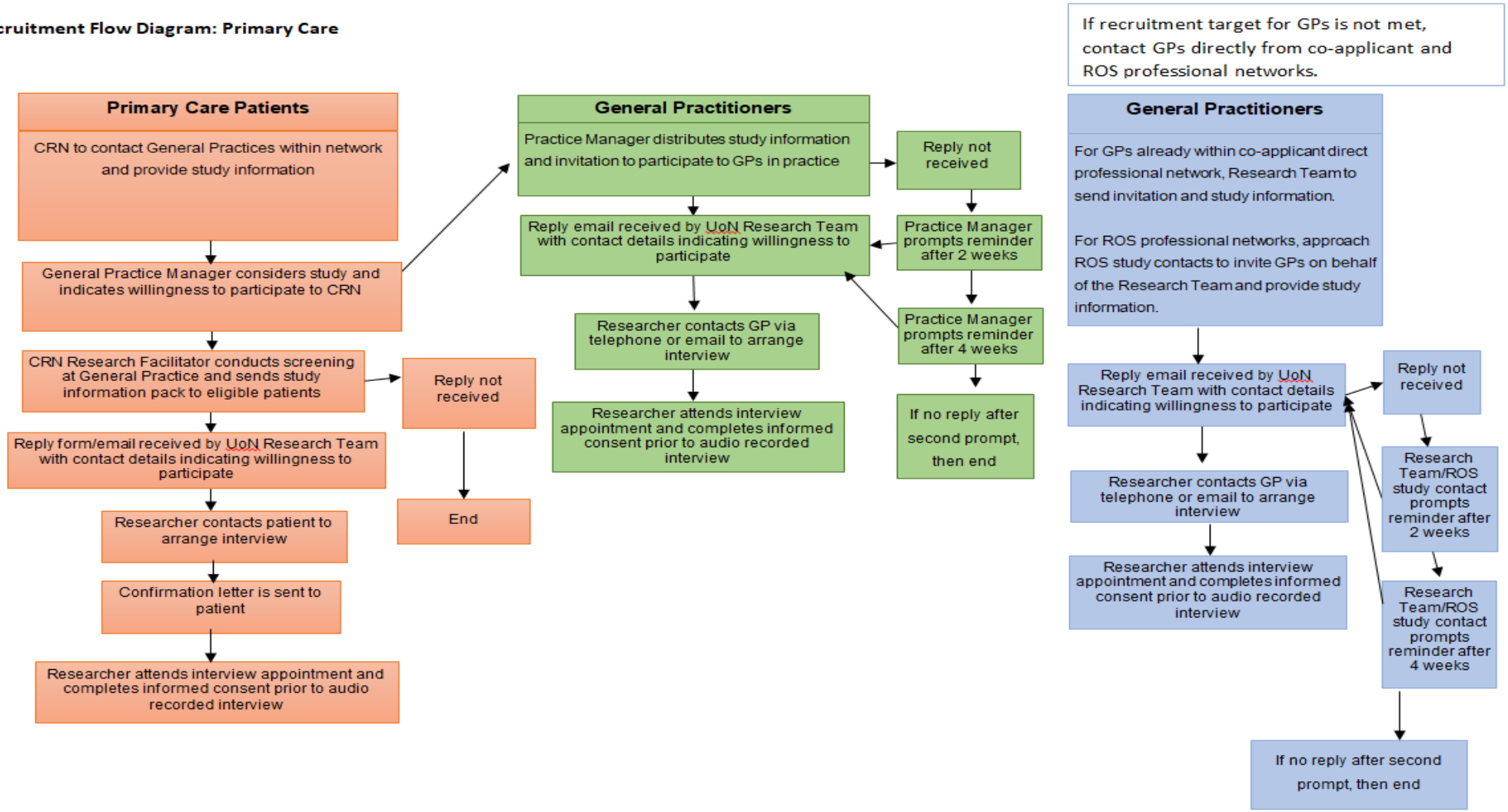

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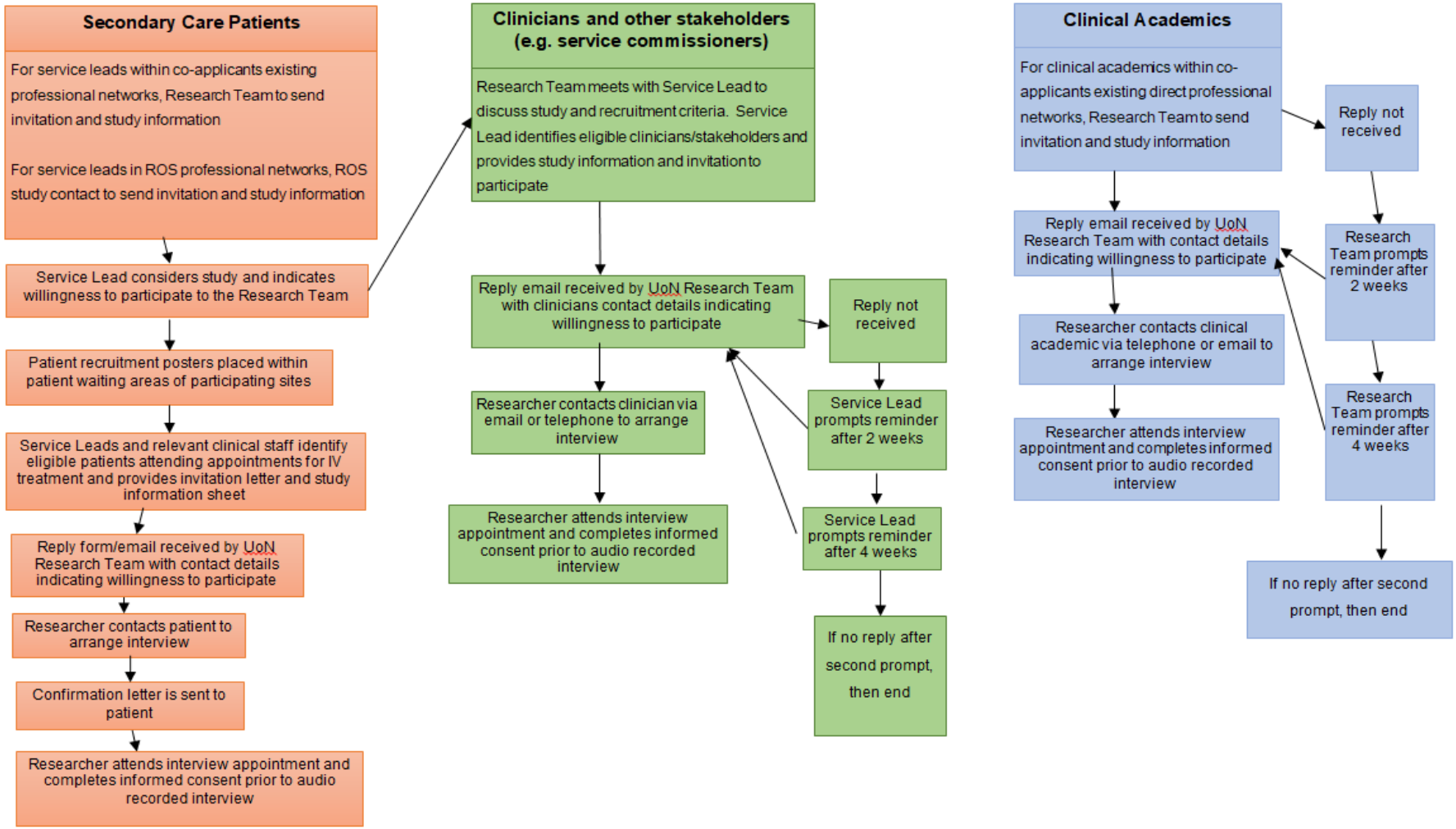

1. BACKGROUND

Osteoporosis is a condition that is characterised by low bone mass and structural deterioration of bone tissue, resulting in bone fragility and susceptibility to fracture - 'fragility fracture' (1). The condition is age-related and particularly common in post-menopausal women. Current NICE guidelines recommend that people with osteoporosis and fragility fracture or with osteoporosis and risk factors indicating high risk of future fracture should be offered bisphosphonate treatment (2). This treatment has been shown to increase bone density and to reduce the risk of fragility fracture by 20-70%, dependent on the site of fracture (3-5).

Alendronate is recommended as the first line bisphosphonate treatment in adults, in England and Wales (2), however, complex dosing instructions are required to support drug absorption and to reduce side effects. This medication is taken orally, once a week, at least 30 minutes before food or other medicines, with a minimum of 200 mls of plain water and patients are recommended to remain upright while taking it and for at least 30 minutes after (6). Taking Alendronate correctly (treatment compliance), is challenging for some patients, in particular older patients on multiple medications and those with underlying cognitive impairment (7-8). Long-term treatment persistence (defined as the cumulative time duration from initiation to discontinuation of therapy) is also poor with Alendronate. The reasons for this are multifactorial, and include scepticism over benefits and safety, lack of understanding of the consequences of non-treatment and risk of or experienced side effects (9-14). In everyday clinical practice, long-term treatment adherence (encompassing both compliance and persistence (15)) with Alendronate is poor, ranging from 16-42% over 2 years (16-17).

Alternative bisphosphonate regimens to Alendronate are available and vary in frequency of use and/or route of administration. These include monthly oral Ibandronate, 3 monthly intravenous Ibandronate, and yearly intravenous Zoledronate. These alternative bisphosphonate regimens have been shown to improve long-term adherence (18-21) however, the most clinically and cost-effective regimen remains unclear. Furthermore, clinicians should also take into account patient understanding, preference and characteristics around medication. What is most cost-effective in clinical trials may not be the most cost-effective or acceptable in everyday clinical practice. Therefore, in keeping with the commissioning brief, a mixed methods research study is needed to explore and ascertain the evidence for effectiveness and cost-effectiveness of the different bisphosphonate regimens compared to Alendronate, as well as capturing the experience and opinions of clinicians and patients.

There is relatively little qualitative literature regarding patient experiences or preferences for bisphosphonate regimens; for example, a systematic review and meta-ethnography of patient experiences of living with osteoporosis reported patient uncertainty about the purpose of medication but no findings relating to experiences of taking bisphosphonates (29-30). Hilligsmann et al reviewed existing quantitative preference studies in 2016 and concluded that patients generally preferred less frequent dosing regimens, but noted variation in preferences (31-32). One important limitation of these discrete choice experiment preference studies is that patients are asked to choose between hypothetical treatments and not real ones, and were limited to 4 attributes (efficacy, side effects, route and frequency of administration). In real-life, other practical attributes, such as where the drug is administered, will also be important to patients. In a more recent qualitative study exploring the reasons for non-adherence, upper gastrointestinal side effects with Alendronate was been graphically described, although anticipation of side effects was as much a deterrent to adherence as was actually experiencing the side effects (33).

For those able to tolerate oral bisphosphonates, various strategies have been proposed to try and improve long term adherence, which include the use of reminders, patient education and treatment monitoring (34- 37). A Cochrane review of strategies to improve treatment adherence highlighted the importance of more frequent patient interactions and regular discussion over compliance issues (38). The International Bone Working Group on treatment adherence recently recommended the routine use of bone turnover markers to aid treatment compliance (39). A preferred alternative to oral bisphosphonates, whether daily, weekly or monthly is an annual, intravenous (IV) infusion of bisphosphonate (Zoledronate). Patients have reported increased satisfaction with Zoledronate, compared with weekly Alendronate and higher long-term adherence (40-41). Administering bisphosphonates intravenously is an obvious strategy to improve compliance and Zoledronate is inexpensive; however, needle phobia, infusion centre costs, side effects, scheduling reminders and the treatment burden of attending hospital for the infusion are potential barriers to long-term persistence. Across Nottinghamshire, to address some of these challenges, Zoledronate is now administered as first line treatment to older patients with fragility fractures directly in their own home (42), with high patient preference and high satisfaction, when compared to the same drug being administered during attendance at a hospital based infusion centre (43). Within central Nottingham, Zoledronate is administered as part of the community osteoporosis service, thereby not only addressing issues around drug administration but issues around patient education, benefits of treatment and long term persistence (44).

The recent HTA systematic review and economic evaluation of bisphosphonates for the prevention of fragility fractures, led by our co-applicants SD and NG (45) and which informed the NICE TA464 guideline (2) concluded that bisphosphonates are effective in preventing fragility fractures, however, the benefit-to-risk ratio in the lowest-risk patients may be debatable given the low absolute QALY gains and the potential for adverse events. Whilst the model was structured to allow direct comparisons between different bisphosphonates, several simplifying assumptions were made that limited the accuracy of the comparisons between the different bisphosphonates treatments. For example, the way in which long-term treatment adherence was modelled may have missed important differences between regimens driven by their varying acceptability to patients, in particular, the duration of treatment and the impact of adverse events were assumed to be equivalent for all oral bisphosphonates whether they are given daily, weekly or monthly. One situation in which this may be problematic is when considering the frequency of gastrointestinal adverse events, which relates to oral administration. Similarly, the adverse events for quarterly IV Ibandronate were assumed to be the same as that for yearly IV Zoledronate. The model also did not explicitly incorporate specific safety side effects such as the risk of atypical femoral fractures associated with long-term bisphosphonates use or the risk of osteonecrosis of the jaw for IV bisphosphonates.

2. RATIONALE

Osteoporosis is a common clinical condition, affecting over three million people in the UK. This leads to weakening of the bones, making them fragile and more likely to fracture. In the UK, there are approximately 536,000 new fragility fractures each year, comprising of 79,000 hip fractures, 66,000 clinically diagnosed vertebral fractures, 69,000 forearm fractures and 322,000 other fractures (i.e. fractures of the pelvis, rib, and other long bones) (22). The health care costs are enormous, estimated at £4.4 billion per year and are expected to rise by 25% over the next 5 years (23), due to an ageing society. Fragility fractures are a life-changing experience with consequent loss of mobility and independence, social isolation, depression, and increased mortality (24-25). Any fragility fracture approximately doubles the risk of another fracture (22).

A key priority of the NHS and NIHR (in its current themed call - complex health needs) is to promote healthy ageing and prevent unplanned hospital admissions. Hip fractures alone account for 85,000 unplanned admissions and 1.8 million bed-days in the UK per year (26). Effective fracture prevention is therefore an important strategy in meeting this aim and would impact favourably on several outcomes that are of importance to patients, including the ability to live independently, pain, disability, and death. Improving long term adherence alone with fracture prevention treatments from 60% to 80% would result in a saving to the NHS of £4.3 million over 5 years for secondary prevention (27-28).

3. RESEARCH QUESTION / AIM(S)

The study will look at how effective different bisphosphonate regimens are compared to Alendronate at preventing fractures, whether the reduction in fracture risk can be achieved at a reasonable financial cost and to establish the acceptability of different approaches to patients.

3.1. Objectives

Comparing alternative regimens of bisphosphonate to the standard regimen of oral Alendronate, in preventing osteoporotic fracture in adults, the main objective is to:

- Understand patients and clinicians' views, experiences and preferences regarding different bisphosphonate treatment regimens, by conducting a scoping literature review followed by semi-structured interviews.

3.2. Outcome

This study will benefit patients, clinicians and the NHS by identifying:

- Which bisphosphonate treatments are most effective at reducing fractures, provide the best value for money and are most acceptable to patients;
- What patients, clinicians and researchers think are the most important research questions to inform future research in this area.

4. STUDY DESIGN AND METHODS OF DATA COLLECTION AND DATA ANALYSIS

The study will be conducted in two stages, Stage 1A and Stage 1B in parallel, followed by Stage 2.

Stage 1A seeks to update the 2016 HTA systematic review and cost-effectiveness analysis of bisphosphonates conducted by our co-applicants (SD & NG) incorporating updated evidence and additional information relating to patient adherence and safety/side effects. Stage 2 aims to co-produce prioritised research questions for further research using stakeholder engagement and consensus.

Stage 1A and Stage 2 will not involve patient recruitment and therefore do not require ethical review.

Stage 1B Qualitative study to explore patient and clinician experiences of current treatment regimens

The aim of this stage will be to elicit patient and clinician experiences of using different bisphosphonate regimens, and understand patient, clinician and other stakeholders (including academics' and commissioners') preferences for alternative bisphosphonates regimens compared to Alendronate. In the first instance, a scoping review will identify published studies assessing views and experiences of bisphosphonate regimens. Following this, semi-structured interviews will be conducted with a range of stakeholders.

We will sample purposively using three different approaches to ensure a range of clinicians, patient, commissioners, service managers and researchers' experiences are elicited. The exact numbers of interviewees to be targeted within each approach will be informed by the scoping review. Recruitment strategies will be discussed and informed by PPI partners.

1. First, we will sample GPs and patients from primary care. Research-ready general practices will be approached via the West Midlands NIHR Clinical Research Network (CRN West Midlands). The potential GP sites identified will be sent an invitation letter and a study information sheet. The CRN has dedicated Research Facilitators for engaging the GP practices which they will normally try to do face-to-face as well as via email. They will request to attend a meeting with the practice (normally the Practice Manager or Lead GP or sometimes a full practice meeting) where they will inform them about the study and discuss any concerns they may have. Following this meeting the practice will then decide if they want to participate or not. Practices that indicate willingness to participate will be asked to nominate GPs for invite to interview and to permit access to patient lists for invites to interview. Access to patient lists for invite to interview will be required by the appointed Research Facilitator from CRN West Midlands, who acts as an agent of the General Practices to support the usual care team in identifying eligible patients. No access to participant identifiable information will be provided to the Research Team at this stage. All potentially eligible patients (persons started on oral bisphosphonates within the last 24 months for prevention of fragility fractures) from recruited general practices will be identified by a search of electronic GP records. The search may be further refined to address purposive sampling, and in response to the findings of the scoping review, for example, to target men, or users of alternative bisphosphonates such as Ibandronate. Lists of potentially eligible patients will be screened by GPs to exclude anyone they think is not appropriate (for example, near to end of life). A Study Information Pack will be sent from the GP to the home address of patients on the screened list. This Study Information Pack will contain an Invitation Letter, a Participant (Patient) Information

Sheet, a reply slip and freepost envelope with the Research Team's return address. Patients who return a reply slip will be contacted to arrange a face–to-face or telephone interview. Estimating an average general practice of 8000 patients will have at least 1% of patients taking oral bisphosphonates (estimate derived from a feasibility search in Keele Academic General Practice), and an estimated response rate of 10%, we will mail up to 25 patients in each of the 8 general practices to achieve a sample of approximately 20 patients and 10 GPs. If insufficient GPs are identified through the CRN approach, the study co-applicant will invite GPs from their existing professional networks and/or ROS networks. If ROS networks are approached, the Research Team will provide the Study Information Pack for the ROS to distribute and therefore no participant identifiable information including contact details will be passed from the ROS to the Research Team without prior consent.

2. Second, we will sample from secondary care for specialist clinicians (nurses, consultants), patients receiving hospital based (intravenous) treatments, clinical academics and commissioners. Clinician, clinical academics/researcher and commissioner respondents will be identified through snowball sampling via invitations from service leads. Service Leads will be identified by existing professional networks of the study co-applicants and/or ROS networks. This approach has been chosen as it may not be clear from externally facing information, who would be most appropriate within each site. It is important to ensure we speak to people who have good knowledge of the bisphosphonate regimens in use, rather than randomly sampling within each site, therefore snowballing is appropriate as it enables us to access engaged healthcare professionals, and include a sample of those engaged in research (as per the HTA brief). Eligible participants identified by the Service Leads will receive a Study Information pack, which will include an Invitation (Clinician) Letter/Email and Participant (Clinician) Information Sheet. Patient respondents will be identified through posters in patient service areas and through direct approaches from clinicians, who can provide the Study (Patient) Information Packs as described in 1. Through this method we aim to recruit approximately 10 clinicians (including researchers) and 15 patients across 2-3 sites.

3. Third, we will sample from two specific areas where different or novel first line bisphosphonate regimens are used. This will include Nottingham, which has pioneered giving intravenous treatment first line in people's homes, and Sheffield, where first line Alendronate is recommended with a programme of blood test monitoring which is not usual practice elsewhere in the UK. In these areas we will utilise sampling/recruitment strategies as described in 2. We will aim to recruit up to 5 clinicians and 10 patients in total from the two sites.

These 3 approaches will cumulatively result in approximately 45 patient interviews and 25 clinician (including researchers) interviews. The semi-structured interviews will be conducted face-to-face or by telephone and are expected to take 40-50 minutes to complete. Face-to-face interviews will be conducted in a private setting either within the site of treatment or at their home in the case of a patient participant, or within the place of work for non-patient participants. Written informed consent will be completed with the researcher and participant prior to the audio recorded interview. The interview guide will be developed iteratively throughout the study to cover issues as identified from the scoping review, as well as wider experiences of service quality and delivery (59-60). This will include questions around patient factors (such as values and health beliefs), service factors (location, accessibility, assurance, and empathy), relational factors (provider patient relations) and medication

factors (dosing complexity, frequency, side effects). Clinician and commissioner interviews will also include barriers to maintain a service around alternative bisphosphonates regimens, as well as changes in service over time.

Interviews will be undertaken by SB and the qualitative Research Fellow (employed by UoN). Interviews will be audio-recorded, given a unique identifying number and sent through a secure file-transfer service (password protected) to be transcribed verbatim by Clayton Research Support, an approved UoN and NUH supplier under confidentiality agreement. Transcripts will then be returned securely to UoN with any identifying information removed. Once the transcript is checked, the audio file will be deleted. Identifiable information (participant names and contact details) will be stored on a UoN secure dedicated web server, with access restricted by user identifiers and passwords. Identifiable information will be kept for one year after the completion date of the project and then destroyed.

Thematic analysis of interview data will be conducted. This will involve familiarisation, identification of a framework, and interpretation, paying particular attention to themes clustered around service variables. The analysis will involve a preliminary phase of more general qualitative data analysis (close reading of transcripts, open coding, identification of themes). Analysis will be undertaken in the first instance by the NUBS Research Fellow alongside and overseen by SB. Emerging themes (with all identifying information removed) will be discussed at appropriate intervals with the wider study management group. The approach will allow for both a-priori and emergent codes to be identified. NVivo software will be used to develop an appropriate coding strategy and framework.

5. STUDY SETTING

This is a multi-site study, taking place in GP practices, hospital premises and patient homes. Further details of how participants will be approached and subsequently participate in the study are given in the sampling and recruitment sections below.

6. SAMPLE AND RECRUITMENT

6.1. Eligibility Criteria

Inclusion and exclusion criterial are provided below:

6.1.1. Inclusion criteria

- Adults over the age of 18 with the ability to give informed consent. There is no maximum age range.

Participants will need to come from the following stakeholder groups:

- GPs
- Patients who started on oral bisphosphonates within the last 24 months for prevention of fragility fractures
- Secondary care specialist clinicians (nurses, consultants) involved in the treatment of osteoporosis

- Patients receiving hospital based (intravenous) bisphosphonate treatments for prevention of fragility fractures who began treatment within the last 24 months
- Clinical academics involved in osteoporosis research
- Specialist clinicians (nurses, consultants) from the osteoporosis service in Nottingham and Sheffield with insight into alternate bisphosphonate treatments
- Patients receiving alternate bisphosphonate treatments for prevention of fragility fractures who began treatment within the last 24 months
- Commissioners involved in osteoporosis services

6.1.2. Exclusion criteria

Exclusion criteria are those who do not fall within the inclusion criteria identified above. Further, we will not include patients who:

- Take bisphosphonate medicines for reasons other than osteoporosis or osteopenia, including patients with an active cancer, primary hyperparathyroidism and Paget's disease;
- Are considered unable to give informed consent;
- Are considered to be near to end of life.

6.2. Sampling

6.2.1. Size of sample

Stage 1B will include approximately 70 participants in total. The exact numbers of interviewees to be targeted within each approach will be informed by the scoping review, but as an indication, we are seeking to recruit;

- 45 patients (20 sampled from primary care, 25 from secondary care)
- 10 General Practitioners
- 10 clinical professionals (doctors, nurses, researchers and commissioners) working in secondary care
- 5 additional clinical professionals working in sites with novel treatment regimes

This sample size has been chosen in line with the aims of the study to provide insight into the acceptability of alternate treatment regimes.

6.2.2. Sampling technique

We will sample purposively using three different approaches to ensure a range of clinicians, patients, commissioners, service managers and researchers' experiences are elicited. The approaches to sample identification for each group are described in the recruitment section below.

6.3. Recruitment

6.3.1. Sample identification

GPs: Research-ready general practices will be approached via the West Midlands NIHR Clinical Research Network (CRN West Midlands). The West Midlands CRN are the most appropriate group to make this initial contact as they have insight into research active GP practices within the region. The potential GP sites will be sent an Invitation Letter and a Study Information Sheet. The CRN has dedicated Research Facilitators for engaging the GP practices which they will normally try to do face-to-face as well as via email. They will request to attend a meeting with the practice (normally the Practice Manager or Lead GP or sometimes a full practice meeting) where they will inform them about the study and discuss any concerns they may have. Practices who are willing to participate will be asked to contact GPs working at the practice with an invitation to participate, which will include a Participant (Clinician) Invitation Letter/Email and Participant (Clinician) Information Sheet. If insufficient GPs are identified through the CRN approach, the study co-applicants will invite GPs from their existing professional networks and/or ROS networks. If ROS networks are approached, the Research Team will provide the Study Information Pack for the ROS to distribute and therefore no participant identifiable information including contact details will be passed from the ROS to the Research Team without prior consent. We will seek to recruit 10 GPs over 8 general practices.

Patients on oral bisphosphonates: This group will be recruited within the GP practices who decide to take part in the study through the approach described above (i.e. following a meeting with West Midlands CRN Research Facilitators). All potentially eligible patients (persons started on oral bisphosphonates for prevention of fragility fractures within the last 24 months) from recruited general practices will be identified by a search of electronic GP records. The search may be further refined to address purposive sampling, and in response to the findings of the scoping review, for example to target men or users of alternative bisphosphonates such as Ibandronate. Access to patient lists for invite to interview will be required by the appointed Research Facilitator from CRN West Midlands, who acts as an agent of the General Practices to support the usual care team in identifying eligible patients. No access to participant identifiable information will be provided to the Research Team at this stage. Lists of potentially eligible patients will be screened by GPs to exclude anyone they think is not appropriate (for example, near to end of life or receiving bisphosphonate medication for a reason other than osteoporosis). A Study Information Pack will be sent to the home address of patients on the screened list. This Study Information Pack will contain an Invitation (Patient) Letter, a Participant (Patient) Information Sheet, a reply slip and a freepost envelope with the Research Team's return address. Patients who return a reply slip will be contacted to arrange a face to face interview (in the patients' own home or in a private room in their GP surgery where available and convenient) or telephone interview. Estimating an average practice of 8000 patients will have at least 1% of patients taking oral bisphosphonates (estimate derived from a feasibility search in Keele Academic General Practice), and an estimated response rate of 10%, we will mail up to 25 patients in each of the 8 general practices to achieve a sample of approximately 20 patients.

Secondary care for specialist clinicians (nurses, consultants) clinical academics and commissioners: Clinician, clinical academics/researcher and commissioner respondents will be identified through snowball sampling via invitations from service leads. Service Leads will be identified by existing professional networks of the study co-applicants and/or Royal Osteoporosis Society (ROS) networks. If ROS networks are used, the Research Team will provide the Study Information Pack for the ROS to distribute and therefore no participant identifiable information including contact details will be passed from the ROS to the Research Team without prior consent. This approach has been chosen as it may not be clear from externally facing information, who would be most appropriate within each site. It is important to ensure we speak to people who have good knowledge of the bisphosphonate regimens in use, rather than randomly sampling within each site, therefore

snowballing is appropriate as it enables us to access engaged healthcare professionals, and include a sample of those engaged in research (as per the HTA brief). Interviews will be conducted in private offices in secondary care facilities close to the participants' normal place of work. We will seek to recruit 10 clinicians or clinical academics from 3 sites.

Patients receiving hospital based (intravenous) bisphosphonate treatments: Patient respondents will be identified through posters in patient service areas and through direct approaches from clinicians to participate in the study during the course of their treatment. Interviews will be conducted in a private room within the secondary care facilities where the patient receives their treatment or in the patient's home where convenient. We will seek to recruit 15 patients from 3 sites.

Specialist clinicians (nurses, consultants) in Nottingham and Sheffield with insight into alternate bisphosphonate treatments: These expert groups will be approached via the existing professional networks of the study co-applicants by the Research Team. This is an appropriate approach to identify respondents with sufficient information power regarding novel treatments. We will seek to recruit 5 clinicians from the 2 sites.

Patients receiving alternate bisphosphonate treatments: Patient respondents will be identified through Study Information Posters in patient service areas and through direct approaches from clinicians at the Nottingham and Sheffield sites where the patients are receiving their treatment. Interviews will be conducted in a private room within the secondary care facilities where the patient receives their treatment or in the patient's home where convenient. We will seek to recruit 10 patients from the 2 sites.

Participants will be offered a high street voucher to the value of £10 for the inconvenience of taking part in the study.

6.3.2. Consent

The process for obtaining participant informed consent will be in accordance with the REC guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced.

Capacity to consent is defined as the patient's ability to understand the purpose and nature of the research; understand what the research involves, its benefits (or lack of), risks and burdens; understand the alternatives to taking part; be able to retain the information long enough to make an effective decision; and be able to make a decision (Mental Capacity Act 2019).

No study-specific interventions will be done before informed consent has been obtained. The investigator or their nominee and the participant shall both sign and date the Consent Form before the person can participate in the study. The participant will receive a copy of the signed and dated forms and the original will be retained in the study records.

The participant will also be informed that entry into the study will be entirely voluntary and that their treatment and care will not be affected by their decision. They will be informed that if they did agree to participate, they can still withdraw at any time, without giving a reason, and that such a decision will not affect future treatment or care, or result in any loss of benefits to which the participant is otherwise entitled.

The investigator will inform the participant of any relevant information that becomes available during the course of the study, and will discuss with them whether they wish to continue with the study. If applicable they will be asked to sign revised consent forms.

If the Consent Form is amended during the study, the investigator shall follow all applicable regulatory requirements pertaining to approval of the amended Consent Form by the REC and use of the amended form (including for ongoing participants).

There will be a different participant information sheet and consent form for the patient and non-patient samples.

7. ETHICAL AND REGULATORY CONSIDERATIONS

7.1. Assessment and management of risk

This qualitative study does not involve any alterations to patient treatment, and participants' involvement in the study will be limited to undertaking a qualitative research interview. It is therefore not anticipated that the study activities will raise the risk of potential for harm to the participants.

If a patient discloses any information during qualitative interviews that suggests they are at risk of harm, or a potential risk of harm to others, the relevant professional with oversight for the patients' care (in most cases the patient's GP) will be contacted urgently, and the patient will be informed. In the case of a safeguarding disclosure from any participant where the most appropriate reporting professional is not easily identified, the report will be made to the Chief Investigator of the study who will advise the most appropriate next step and the participant will be informed.

If a patient discloses any concerns or questions over their care, or wishes to discuss changes in their care, the researcher will advise the patient to discuss this further with their GP or secondary care clinician.

If any participant has any concerns or questions regarding the study that cannot be answered by the researcher, they will be advised to contact the sponsor.

7.2. Research Ethics Committee (REC) review & reports

The study will not be initiated before the protocol, consent forms and participant information sheets have received approval / favourable opinion from an NHS Research Ethics Committee (REC) (as required), respective National Health Service (NHS) or other healthcare provider's Research & Development (R&D) department, and the Health Research Authority (HRA) if required. Should a protocol amendment be made that requires REC approval, the changes in the protocol will not be instituted until the amendment and revised informed consent forms and participant information sheets have been reviewed and received approval / favourable opinion from the REC. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the REC are notified as soon as possible and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed.

An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the study is declared ended. If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination. Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice, and the Department of Health Research Governance Framework for Health and Social care, 2005.

7.3. Peer review

This study has been peer reviewed through two rounds of review by the National Institute of Health Research (NIHR) Health Technology Assessment Panel prior to research funding being agreed. Further information on the NIHR expert review process is available through the NIHR website (https://www.nihr.ac.uk/documents/).

7.4. Patient & Public Involvement

We are working closely with the ROS UK - the only UK wide charity dedicated to improving the care of people with osteoporosis - and the Nottingham ROS (NotROS) Support Group. The NotROS has 250 members in Nottingham, actively involved in fund raising events, local awareness campaigns, and educational update meetings, closely aligned to the ROS. Supporting research features highly within the NotROS group and a number of patients are currently involved as research lay members.

Following the commissioned call, we have undertaken 2 focus groups, one with the ROS (n=3) and one with the NotROS (n=7), who have influenced the design of this application (suggestion of interviews with service users and service commissioners), choice of study outcomes and will be involved throughout the study. The ROS and 2 members of the NotROS have agreed to be co-applicants, all of whom have previous research experience.

In addition, both of our co-applicants from the NotROS have had a range of alternative bisphosphonate treatments over the last 10 years, from daily Alendronate, weekly Alendronate, monthly Ibandronate to more recently IV Zoledronate (both as a day case attendee in hospital and the community IV Zoledronate service at home).

Our PPI groups will be closely involved in the further management of the research, developing

participant information resources, contributing to the reporting of the research and dissemination of research findings. More specifically, the ROS will take a leading role in convening the stakeholder events, to ensure these are nationally representative (Stage 2). AD (Acting Executive Director-Service Delivery) has agreed to be a co-applicant. AB and MH are named co-applicants for the NotROS group and will work with the SMG throughout the project. Their experiences as patients suffering with osteoporosis and access to services will be invaluable in better understanding the patient journey. AB and MH will also draw on the wider views of the NotROS 250 patient membership, as required. This may include asking other members to become involved and acting as a further platform for PPI involvement. PPI members from the NotROS group will undergo the standard hospital PPI training programme, further supported by the hospital PPI team (costed in appropriately).

7.5. Regulatory Compliance

The study will be conducted according to the Quality Management System of the sponsor. The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 2013; the principles of Good Clinical Practice, and the UK Policy Framework for Health and Social Care Research 2017.

Before any site can enrol patients into the study, the Chief Investigator/Principal Investigator or designee will apply for HRA approval for the study and will make contact with all potential site Principal Investigators, R&D departments and, if applicable, the local Clinical Research Network.

All researchers collecting data within study sites will have a valid research passport, with a copy lodged with the sponsor within the study documents.

Prior to commencing recruitment, sites must confirm their capacity and capability to conduct the study, as per the HRA approval letter.

Should it be considered that any amendments may potentially affect a site's capacity to continue in the study, the Chief Investigator/ Principal Investigator or designee will inform the Sponsor of the proposed amendment. The amendment will be submitted as per Section 8.7.

7.6. Protocol compliance

Protocol deviations, non-compliances, or breaches are departures from the approved protocol. Accidental protocol deviations can happen at any time. They will be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately. Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

7.7. Amendments

It is the sponsor's responsibility to decide whether an amendment is substantial or non-substantial for the purposes of submission to the REC. If the sponsor wishes to make a substantial amendment to the REC application or the supporting documents, the sponsor must submit a valid notice of amendment to the REC for consideration. The REC will provide a response regarding the amendment within 35 days of receipt of the notice, informing the HRA of the amendment. Site R&D departments will also need to be provided with the information on the amendment in order to assess the implications for their site and involvement. Their level of review will be dictated by the category as assessed by the REC or HRA (A, B or C). Guidance on the categorisation of amendments for studies

involving the NHS can be found on the HRA website (http://www.hra.nhs.uk/resources/after-you-apply/amendments/).

If applicable, other specialist review bodies (e.g. CAG) need to be notified about substantial amendments in case the amendment affects their opinion of the study.

Non-substantial amendments also need to be notified to the HRA as well as the relevant R&D departments of participating sites to assess whether the amendment affects the continued capacity for that site. Note that some amendments that may be considered to be non-substantial for the purposes of REC and/or MHRA may still need to be notified to NHS R&D (e.g. a change to the funding arrangements).

7.8. Adverse Event

The occurrence of an adverse event as a result of participation within this study is not expected and no adverse event data will be collected.

7.9. Data protection and patient confidentiality

All study staff and investigators will endeavour to protect the rights of the study's participants to privacy and informed consent, and will adhere to the Data Protection Act 2018 and the General Data Protection Regulation 2018 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Regulation's core principles. Study documents will only collect the minimum required information for the purposes of the study. Study documents will be held securely, in a locked room, or locked cupboard or cabinet. Access to the information will be limited to the study staff and investigators and any relevant regulatory authorities (see above). Computer held data including the study database will be held securely and password protected. All data will be stored on a secure dedicated web server. Access will be restricted by user identifiers and passwords (encrypted using a one way encryption method).

During data collection, all study staff will follow a standard procedure for the handling of study information and the transfer of information between study partners, with a Working Practice Document for Handling Audio Files within the study documents. Following invitation to participate (procedure outlined in 6.3.1), willingness to participate replies will be collated at UoN. Interviews will be arranged and carried out by the qualitative research team within UoN, including following procedures for informed consent. Following interview, consent forms will be stored with the study documents in a locked cupboard/cabinet. The study participant will be given a unique identifying number, and this will be entered into a study recruitment spreadsheet stored at UoN, with the updated copy transferred via email within a password protected document to NUH (password agreed face to face between study team at UoN and NUH) to be stored in the study archive. The interview recording will be sent to the transcription service (Clayton Research Support) by secure file transfer protocol with the password sent in a separate email. During transcription, all further identifying information will be removed. All audio recordings will be destroyed immediately after transcription has been completed and checked for accuracy. Transcriptions will be held on a secure server at UoN for the duration of the study for the purposes of data analysis, with a copy of the transcript transferred by within a password protected document via email to NUH to be stored in the study archive. Identifiable information (participants name and contact details) will be kept for one year following the completion of the study and then destroyed. Non-identifiable study data will be kept for a minimum of five years following completion of the study. Electronic data will be backed up every 24 hours to both local and remote media in encrypted format.

Monitoring of study data shall include confirmation of informed consent; source data verification; data storage and data transfer procedures; local quality control checks and procedures, back-up and disaster recovery of any local databases and validation of data manipulation. The Study Coordinator, or where required, a nominated designee of the Sponsor, shall carry out monitoring of study data as an ongoing activity.

Study data and evidence of monitoring and systems audits will be made available for inspection by relevant REC as required.

In compliance with the ICH/GCP guidelines, regulations and in accordance with the NHS Code of Research Conduct and Research Ethics, the Chief Investigator will maintain all records and documents regarding the conduct of the study. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility. The CI and research staff involved with this study will 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 will be obtained for the disclosure of any said confidential information to other parties.

7.10. Indemnity

As Nottingham University Hospitals NHS Trust is acting as sponsor for this study, NHS indemnity applies. NHS bodies are legally liable for the negligent acts and omissions of their employees. Non-negligent harm is not covered by the NHS indemnity scheme. The Nottingham University Hospitals NHS Trust, therefore, cannot agree in advance to pay compensation in these circumstances. In exceptional circumstances an ex-gratia payment may be offered.

7.11. Access to the final study dataset

In compliance with ICH/GCP guidelines, regulations and in accordance with the Nottingham University Hospitals NHS Trust standard operating procedures (SOP) and Research Ethics, the CI will maintain

all records and documents regarding the conduct of the study. The study documents held by the Chief Investigator on behalf of the Sponsor shall be finally archived at secure archive facilities at Nottingham University Hospitals. This archive shall include all anonymised interview transcripts, study databases and associated meta-data encryption codes. These will be retained for at least 5 years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.

The CI will have primary access to the final study dataset. The CI will also designate core members of the study team access to the dataset.

8. DISSEMINATION POLICY

8.1. Dissemination policy

The study's dissemination strategy aims to target these groups.

A) Policy makers, commissioners, operational managers, change agents and healthcare professionals:

These will be the most important dissemination groups and, in this respect, the ROS will take a leading role, working closely with the research team and the NotROS Support Group.

- *Disseminating outputs to policy makers, commissioners, operational managers and change agents*
  The commissioning landscape is changing with CCGs working together in communities that express their aims and priorities through plans for integrated care, including the integration of falls and fracture prevention services such as FLS. It is our assessment that the precise arrangements for policy planners and commissioning, including job roles, organisational structure and funding flows will change during the course of the study. We will therefore adopt a flexible approach to dissemination, led by the ROS, which has the skills and capacity in this area. Key events will be targeted such as policy maker, commissioner and healthcare manager bespoke regional meetings (aiming dissemination at 3 events) and webinars (aiming dissemination at 3 events).

- *Disseminating outputs to health professionals*
  There is a well-developed and well-motivated cohort of clinicians working in the field of osteoporosis, secondary fracture prevention and FLS. The ROS has a team of professionals and a set of networks and activities already in place that engages with this community.

- *Wider internet awareness*
  We will submit articles to various periodicals and updates to relevant websites such as the Health Service Journal and NHS Primary Care Commissioning.

B) Researchers:

A publication policy will be agreed with all co-applicants and a systematic plan, including authorship, for the peer reviewed publications. Methodology papers including those describing the development of methodology, health economics and the protocol are likely to be targeted at major online free to access journals, such as Trials. The full study report will be available on the NIHR website. Publication of the completed study paper will be aimed at high impact journals, for example British Medical Journal (BMJ), Osteoporosis International and Journal of Bone and Mineral Research (JBMR) and other papers in the appropriate high impact general or specialist health economic journals. Results from the study will also be submitted for presentation at scientific meetings and conferences targeted at clinicians working with older people, for example British Geriatrics Society scientific meeting and the Fragility Fracture Network.

C) User Groups:

We will work with our PPI Group on the study's dissemination and engagement strategy with the public. This will include publishing articles in their dedicated newsletter and using their direct links to the Royal Osteoporosis Society (https://www.ros.org.uk).

D) Networks and the NIHR Faculty:

Involvement with the Clinical Research Network (CRN) will allow further dissemination of the findings through established network routes and provide a significant contribution to the collective research endeavour of the NIHR.

8.2. Authorship eligibility guidelines and any intended use of professional writers

A publication policy will be agreed with all co-applicants and a systematic plan, including authorship, for peer reviewed publications. Criteria for authorship will be in accordance with the International Committee of Medical Journal Editors. Individuals who have contributed to the study but not fulfilled the authorship criteria will be acknowledged in a separate section.

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10. APPENDICES

10.1. Appendix 1 - Required Documentation

GP Network Invitation Letter with reply slip v1.0

Participant Information Sheet (PIS) Patient v1.0

Participant Information Sheet (PIS) Clinician v1.0

The BLAST OFF Study Poster v1.0

Patient Consent Form v1.0

Clinician Consent Form v1.0

Interview Schedule Draft Clinicians and GPs v1.0

Interview Schedule Draft Primary Care Patients v1.0

Interview Schedule Draft Secondary Care Patients v1.0

GP Patient in Study Letter v1.0

Service Lead Invitation Letter v1.0

Clinician and Stakeholder Invitation Letter v1.0

BLAST OFF Working Practice Document Audio Files Control v1.0

10.2. Appendix 2 – Schedule of Procedures

Design	Stage 1B	Dissemination
Stage 1A – Systematic Review		
Stage 1B - Qualitative study	X	
Scoping Reviews	X	
Semi-structured interviews:	X	
CRN to contact G.P practices	X	
G.P Practice to produce patient list, post patient invitation packs.	X	
Researchers to contact respondants	X	
Primary care GPs & Patient Interviews	X	
Informed consent	X	
Secondary care Clinicians & patients Interviews	X	
Novel regimens Clinician & patients Interviews	X	
Stage 2: Stakeholder Engagement:		
Step 1: Subgroup Review		
Step 2: Stakeholder groups		
Step 3: Prioritisation Workshop		
Researchers Publication		X
Networks & NIHR Dissemination		X
Commissioners, ROS, MDT, Patients & public		X

10.3. Appendix 3 – Amendment History