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Novartis Research and Development

KJX839/Inclisiran

Clinical Trial Protocol CKJX839A1GB01 / NCT04807400

Title: A phase IIIb, multicentre, randomised controlled study to evaluate the implementation, preference and utility for administration of inclisiran sodium in participants with Atherosclerotic Cardiovascular Disease (ASCVD) or ASCVD-risk equivalents and elevated Low Density Lipoprotein Cholesterol (LDL-C) using a primary care models in the NHS

Short Title: VICTORION-Spirit - Study in Primary care evaluating Inclisiran deliveRy Implementation + enhanced SupporT *(Spirit)*

Document type:	Clinical Trial Protocol
EUDRACT number:	2020-004401-31
Version number:	02 (Amended Protocol)
Clinical Trial Phase:	IIIb
Release date:	12 Sep 2022

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List of abbreviations

AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ASCVD	Atherosclerotic Cardiovascular Disease
ASGPR	asialoglycoprotein receptor
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
[redacted]	[redacted]
CFIR	Consolidated Framework for Implementation Research
CI	Confidence Interval
CDM	Clinical Data Management
CHD	Coronary Heart Disease
CK	Creatinine Kinase
CMO&PS	Chief Medical Office and Patient Safety
COA	Clinical Outcome Assessment
CQA	Clinical Quality Assurance
CRA	Clinical Research Associate
CRO	Contract Research Organisation
CSR	Clinical study report
CSQ-8	Client Satisfaction Questionnaire
CT	Computerised tomography scan
CTC	Common Terminology Criteria
CV	coefficient of variation
DMC	Data Monitoring Committee
[redacted]	[redacted]
eCRF	Electronic Case Report Form
EHR	Electronic Health Record
EMA	European Medicines Agency
EMR	Electronic Medical Record
EOS	End of study
EQUATOR	Enhancing the QUAlity and Transparency Of health Research
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
FARSITE	NWEH's Feasibility Assessment and Recruitment System for Improving Trial Efficiency system
FAS	Full Analysis Set
FDA	Food and Drug Administration
FH	Familial Hypercholesterolaemia
GalNAc	N-acetylgalactosamine
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	Gamma-glutamyl transferase

GLDH	Glutamate dehydrogenase
GM	Greater Manchester
GP	General Practitioner
HCP	Health Care Professional
[redacted]	[redacted]
[redacted]	[redacted]
HeFH	Heterozygous Familial Hypercholesterolaemia
IB	Investigator's Brochure
EU	European Union
IDMC	Independent Data Monitoring Committee
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IN	Investigator Notification
INR	International Normalised Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
LDL-C	Low-density Lipoprotein associated Cholesterol
LDLR	LDL Receptors
LFT	Liver function test
LLN	lower limit of normal
MDCO	The Medicines Company
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram(s)
mL	Milliliter(s)
MRI	Magnetic resonance imaging
NCDS	Novartis Clinical Data Standards
NHS	UK National Health Service
NHS-E	National Health Service- England
NWEH	NorthWest EHealth
PAI	Physical Activity Index
PAM	Patient Activation Measure
PCR	Polymerase Chain Reaction
PCSK9	Proprotein convertase subtilisin/kexin type 9
PFS	Pre-filled Syringe
PI	Principal Investigator
PIS	Patient Information Sheet
PROM	Patient Reported Outcome Measure
PSSRU	Personal Social Services Research Unit
QMS	Quality Management System

QOPH	Quality and Outcomes in Primary Healthcare clinical indicators
RAP	The Report and Analysis Plan
REB	Research Ethics Board
[redacted]	[redacted]
RISC	RNA-induced silencing complex
RNAi	Ribonucleic acid interference
s.c.	Subcutaneous
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
siRNAs	small interfering RNAs
SOP	Standard Operating Procedure
Spirit	Study in Primary care evaluating Inclisiran deliveRy Implementation + enhanced SupporT
SRQR	Standards for Reporting Qualitative Research
SDTM	Structured Data Tabular Model
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAEs	Treatment Emerged Adverse Events
TIDieR	Template for Intervention Description and Replication
TD	Study Treatment Discontinuation
TBL	Total bilirubin
[redacted]	[redacted]
[redacted]	[redacted]
UK	United Kingdom
ULN	upper limit of normal
ULQ	upper limit of quantification
US	Ultra Sound
UTI	Urinary Tract Infection
WHO	World Health Organisation
WoC	Withdrawal of Consent

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Cohort	A specific group of participants fulfilling certain criteria and generally treated at the same time
ConneXon	A suite of software applications developed by NWEH to support the operation of Real World Evidence clinical trials.
Control drug	A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained
Estimand	A precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarises at a population-level what the outcomes would be in the same patients under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest (e.g. treatment discontinuation, use of prohibited medications, deviation in background treatment or death).
Investigational drug/ treatment	The drug whose properties are being tested in the study - KJX839/Inclisiran for Injection (sub-cutaneous use), is a sterile formulation of inclisiran sodium in water for injection packaged in vial or glass pre-filled syringe (PFS) presentations; also referred to as study drug
Medication number	A unique identifier on the label of medication kits
Mis-randomised participants	Mis-randomised participants are those who were not qualified for randomisation and who did not take study treatment, but have been inadvertently randomised into the study
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Part	A sub-division of a study used to evaluate specific objectives or contain different populations. For example, one study could contain a single dose part and a multiple dose part, or a part in participants with established disease and in those with newly-diagnosed disease
Participant	A trial participant (can be a healthy volunteer or a patient)

Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Premature participant withdrawal	Point/time when the participant exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned
Randomisation number	A unique identifier assigned to each randomised participant
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant
Study treatment	The study treatment, KJX839/Inclisiran for Injection (sub-cutaneous use), is a sterile formulation of inclisiran sodium in water for injection packaged in vial or glass pre-filled syringe (PFS) presentations
Study treatment discontinuation	When the participant permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Treatment of interest	The treatment of interest and, as appropriate, the alternative treatment to which comparison will be made. These might be individual interventions, combinations of interventions administered concurrently, e.g. as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing the related clinical question of interest, which might or might not be the same as the study treatment.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of study consent (WoC)	Withdrawal of consent from the study occurs only when a participant does not want to participate in the study any longer and does not allow any further collection of personal data

Amendment 2

Amendment rationale

The study CKJX839A1GB01 was initiated in July 2021 with the first patient enrolled on 07 July 2021. As of 15th July 2022, 900 patients have been randomised.

The main purpose of the amendment is to:

a. Updated the definition of investigational treatment and intercurrent events

b. Corrected typographical errors some of which had been notified to the ethics committee previously

c. Corrected the use of the word placebo to standard of care + behavioural support

d. Confirmed the inclisiran group is inclisiran (+/- behavioural support)

e. Confirmed that if questionnaires are not returned they will be followed up twice at 2-weekly intervals

f. Confirmed that patients will be monitored for safety events for 30 days after their EOS visit and not administration of study treatment

g. Confirmed that the data analysis in the protocol summary will be from baseline to Day 270 and not Day 90, this now matches section 12.4.1

Changes to the protocol

The changes made to the protocol, and sections affected are listed below

Section	Changes made
Glossary of terms	Update to investigational drug/ treatment and intercurrent events
Amendment 1 - changes to the protocol - exclusion criteria	Key exclusion criteria for triglycerides updated
Amendment 1 - changes to the protocol - section 5.2	Exclusion criteria for triglycerides updated
Amendment 1 - changes to the protocol - section 6.1	Corrected that patients do not need to wait 15 mins after receiving the Inclisiran dose at Day 1
Protocol summary – treatment of interest	Updated ratio to confirm this is 1:1:1
Protocol summary – data analysis	Corrected inclisiran and placebo to inclisiran (+/- behavioural support) and standard of care + behavioural support and confirmed we are looking at changes from baseline to Day 270
4.5 – treatment groups and outcome assessments	Confirmed patients will attend 3 study visits Confirmed visits will be planned in accordance with the assessment schedule Confirmed the behavioural support programme is delivered monthly Confirmed – Unreturned questionnaires will be followed up twice at 2-weekly intervals.
6.1.3 – Treatment groups	Confirmed the ratio is 1:1:1
6.4.1 - treatment compliance	confirmed participants will receive monthly telephone based behavioural support
8.1 - Domiciliary visits	Confirmed these will be conducted by experienced HCPs
Table 8.1	Confirmed the behavioural support will be a scheduled programme of delivery
9.2 - Study completion and post-study treatment	Confirmed that patients will be remotely monitored for safety events for 30 days after their EOS visit
10.3.3 SAE reporting	Confirmed that SAEs will be reported for 30 days after their EOS visit
11.2 - Database Management and quality control	Confirmed that IRT data will be sent electronically to Novartis and NWEH at specific timelines
12.4.1 - Definition of primary endpoint	Confirmed test treatment inclisiran (+/- behavioural support) and standard of care + behavioural support and not versus placebo Confirmed the strategy for handling intercurrent events
12.4.2 - Statistical model, hypothesis, and method of analysis	Confirmed test treatment inclisiran (+/- behavioural support) and standard of care + behavioural support and not versus placebo
12.8 - Sample size calculation	Confirmed the sample size would inclisiran group (+/- behavioural support) and standard of care + behavioural support and not placebo

Amendment 1

Amendment rationale

The study CKJX839A1GB01 was initiated in July 2021 with the first patient enrolled on 07 July 2021. As of 9th Sep 2021, 47 patients have been randomised.

The main purpose of the amendment is to:

a. Remove the DMC and need for interim analysis

- When the study was written we did not have a licence for the IMP therefore a DMC was a requirement at the time. We are administering the IMP as it should be given and within its license.

b. Addition of exclusion for patients with triglycerides greater than or equal to 4.52

- We are unable to calculate LDL-C values using the Friedewald formula if triglyceride value is high

c. Added that patients randomised to Group 1 will not be required to attend the Day 1 visit but can receive a phone call instead. Visit schedule has also been updated

- Group 1 patients do not receive IMP and no additional assessments are required at this visit

d. Reworded primary objective as this was not very clear

- The primary objective of this study is to demonstrate superiority of inclisiran +/- behavioural support compared to standard of care + behavioural support in a primary care setting, in terms of the percentage change in LDL-C from baseline to Day 270 in adults with elevated LDL-C.

e. [redacted]

f. If patients receive the study medication at home the lipid profile test will also need to be performed at Day 90

- This is to ensure all study assessments are performed as per protocol

g. COVID-19 vaccine should not be given within 7 days of receiving IMP.

- Delivery of COVID-19 vaccine is a change in Novartis policy

h. [redacted]

i. The site of injection is the abdomen, alternative injection sites include the upper arm or thigh.

- When the protocol was written the IMP was not licensed so this information was not available

j. The Behavioural Support Programme consists of a telephone based support service providing advice on diet, lifestyle, medication adherence and CV risk management. Patients will have access to this service throughout the study

- This has been updated as it is not when patients choose but a scheduled programme of delivery

k. Update on requirements for adverse events

- In this study, only SAEs will be detected, documented and reported. AEs leading to treatment discontinuation will be documented only and do not need to be reported as per normal practice

l. Reference to safety management plan removed

- This is an internal document that will not be given to sites and is not part of the protocol

m. Pregnancy reporting section updated

- This now reflects the legally approved wording as per the pregnancy PICF

n. [redacted]

o. Confirmation that the behavioural support programme will be delivered by health advisors and not healthcare professionals

p. [redacted]

q. Removal of liver events

- This is consistent with the design of the study being to understand the effects of the innovation within the real world conditions of everyday clinical practice, there was no requirement to include testing in the study or monitoring of renal or hepatic function required in accordance with our SPC.

r. Update to the number of interviews that may be required

- This is to give some more scope in case we haven't reached data saturation by the 30/10 interviews

s. Update to lipid profile in schedule of events

- To match section 8.4 of the protocol

t. Confirmation that study treatment refers to Inclisiran

Changes to the protocol

The changes made to the protocol, and sections affected are listed below

Section	Changes Made
Title page	Short title updated so the underlined letters spell SPIRIT
Glossary	Definition of study treatment updated
Protocol summary – primary objective	Updated wording
Protocol summary- Key exclusion criteria	Exclusion added for patients with triglycerides value greater than or equal to 4.52 mmol/l
Protocol Summary - Data Analysis	Wording updated
Section 3.1	Wording updated
Section 4.2	[redacted]
Section 4.3.1.2	Updated the number of interviews
Section 4.3.2.2	Updated the number of interviews
Section 4.3.3.2	Updated the number of interviews
Section 4.5	Added that Patient's randomised to Group 1 do not need to attend the Day 1 visit but can receive a phone call instead Typo corrected References to DMC have been removed If patients receive the study medication at home the lipid profile test will also need to be performed at Day 90
Section 5.2	Exclusion added for patients with triglycerides value greater than or equal to 4.52 mmol/l
Section 6.1	Added clarification on time between receiving COVID-19 Vaccine and study medication
Section 6.1.5	Updated with regards how the automated data will be collected
Section 6.5.2	Updated information on the injection site

Section 7.1	Text updated to match section 4.3
Section 8	Confirmed access to the behavioural support programme is a scheduled programme of delivery
Table 8.1	Assessment schedule updated
Section 8.5.2	Reference to DMC has been removed
Section 9.1.1	Reference to liver and renal safety has been removed
Section 10.2	Updated wording to reflect normal practice of AE reporting Removed reference to the safety management plan
Section 10.3.4	Updated wording on how pregnancies will be followed
Section 10.4.1	Removed reference to DMC
Section 12.4.2	Updated wording
Section 12.6	[redacted]
Section 12.7	Confirmed there will be no interim analyses
Section 16.1	Updated that behavioural support programme will be delivered by health advisors
Section 16.4	[redacted]

Protocol summary

Protocol number	CKJX839A1GB01
Full Title	A phase IIIb, multicentre, randomised controlled study to evaluate the implementation, preference and utility for administration of inclisiran sodium in participants with Atherosclerotic Cardiovascular Disease (ASCVD) or ASCVD-risk equivalents and elevated Low Density Lipoprotein Cholesterol (LDL-C) using a primary care models in the NHS.
Brief title	VICTORION-Spirit: Study in Primary care evaluating Inclisiran deliveRy Implementation + enhanced SupporT
Sponsor and Clinical Phase	Novartis, Phase IIIb
Investigation type	Drug
Study type	Interventional, open label
Purpose and rationale	The implementation research study described in this protocol is designed to provide and assess evidence for the implementation of inclisiran within a primary care setting in the NHS. The protocol describes an established implementation science approach utilising a Type 1 hybrid design. The study will focus on testing a clinical intervention in the appropriate real-world situation (in this case primary care) while observing and gathering information on its 'implementability'. The study can therefore be divided into three main elements: • A prospective phase IIIb intervention with inclisiran +/- behavioural support compared to standard of care + behavioural support in a type 1 hybrid implementation design in a primary care population. • [redacted] • A process evaluation that will ascertain the views of patients and healthcare providers about the service they have received or provided and its potential transactability across the NHS.
Primary Objective(s)	The primary objective of this study is to demonstrate superiority of inclisiran +/- behavioural support compared to standard of care + behavioural support in a primary care setting, in terms of the percentage change in LDL-C from baseline to Day 270 in adults with elevated LDL-C.
Secondary Objectives	The secondary objectives of this study are to evaluate the implementation of inclisiran +/- behavioural support compared to standard of care + behavioural support in a primary care setting using the following assessments: • Measures of patient satisfaction using the validated CSQ-8 (Client Satisfaction Questionnaire) administered after treatment at day 90.

	• Measures of patient activation and empowerment using the validated Patient Activation Measure (PAM) questionnaire administered after treatment at day 90. • Measures of adherence to cardiovascular disease self-management using the validated Patient Activation Measure (PAM) questionnaire administered after treatment at day 90 and using assessment of medication adherence during the study period. • A process evaluation conducted using the Consolidated Framework for Implementation Research (CFIR) which will explore inclisiran delivery at three levels: o Feasibility and acceptability of delivery models for inclisiran to patients o Feasibility and acceptability of delivery models for inclisiran to providers (inner setting) o Wider 'transactability' of the proposed delivery models (outer setting) o The service costs of each delivery model o The acceptability and perceived sustainability of patient identification and referral routes • Serious adverse event profile
Study design	A phase IIIb, multicentre, randomised controlled study to evaluate the implementation, preference and utility for administration of inclisiran sodium in participants on established lipid lowering medication or, have been recommended lipid lowering therapy by their healthcare provider but are unable to tolerate treatment, with elevated low density lipoprotein cholesterol (LDL-C) in a primary care population. 900 eligible participants will be randomised (300 per treatment group) at up to 30 primary care centres across Greater Manchester. Eligibility and recruitment to the study will be optimised by using NWEH's proven Feasibility Assessment and Recruitment System for Improving Trial Efficiency (FARSITE) for identification and recruitment at participating GP practices. At the baseline visit/screening on receipt of a signed consent form, eligible participants will be randomised to one of the three treatment groups: • **Group 1:** Participants will continue to receive their background lipid lowering therapy plus behavioural support • **Group 2:** Participants will continue to receive their background lipid lowering therapy, plus inclisiran for injection (delivered in an injection-only model). • **Group 3:** Participants will continue to receive their background lipid lowering therapy, plus inclisiran for injection, plus behavioural support. The study duration will be approximately 9 months.
Study population	The population of interest is adult participants with elevated cholesterol who are receiving treatment with established lipid lowering medication or, have been

	recommended lipid lowering therapy by their healthcare provider but are unable to tolerate treatment. 900 participants (300 per treatment group) at up to 30 primary care centres in the localised geographical region of Greater Manchester will be required for this study.
Key Inclusion criteria	• Male or female participants ≥18 years of age. • Patients on established lipid lowering medication or, have been recommended lipid lowering therapy by their health care provider but are unable to tolerate treatment. • A total cholesterol measurement at screening that is ≥4 mmol/L [approximately 160 mg/dL]. • Participants on lipid-lowering therapies should be on a stable dose for ≥30 days before screening with no planned medication or dose change.
Key Exclusion criteria	1. A triglyceride measurement at screening that is ≥4.52 mmol/L 2. Medical or surgical history that might limit the individual's ability to take study treatments for the duration of the study and/or put the participant at significant risk (e.g. severe respiratory disease; cancer or evidence of spread within approximately the last 5 years, other than non-melanoma skin cancer; or history of alcohol or substance misuse). 3. Current or planned renal dialysis or transplantation. 4. Acute coronary syndrome or stroke less than 4 weeks before the screening visit. 5. Coronary revascularization procedure planned within the next 6 months 6. Women of child-bearing potential (unless using adequate contraception) 7. Previous, current or planned treatment with a monoclonal antibody targeting PCSK9, or with a drug known to be contra-indicated with inclisiran. 8. Previous exposure to inclisiran or participation in a randomised study of inclisiran. 9. Current or previous participation in a clinical study with an unlicensed drug or device within 30 days or five half-lives of the screening visit, whichever is longer.
Study treatment	The study treatment, KJX839/Inclisiran for Injection (sub-cutaneous use), is a sterile formulation of inclisiran sodium in water for injection packaged in vial or glass pre-filled syringe (PFS) presentations
Treatment of interest	Participants will be assigned to one of three of the following treatment groups in a ratio of 1:1:1. **Group 1:** Participants will continue to receive their background lipid lowering therapy plus behavioural support **Group 2:** Participants will continue to receive their background lipid lowering therapy, plus inclisiran for injection (delivered in an injection-only model).

	Group 3: Participants will continue to receive their background lipid lowering therapy, plus inclisiran for injection (delivered in an injection-only model), plus behavioural support.
Efficacy assessments	A capillary blood sample will be taken for immediate analysis of the participant's lipid profile [redacted] for assessment of efficacy. This will be performed at screening/baseline visit, day 90 and end of study (EOS) visit. Parameters to be assessed include: [redacted] • Non-HDL (calculated) • LDL-C calculated using Friedewald
Key safety assessments	Adverse events will be collected throughout the study period using ConneXon data platform. The AEs to be recorded are: • All SAEs whatever the causal relationship to the to the Investigational Medicinal Product (IMP) or to a procedure required by the study protocol • AEs leading to treatment discontinuation
Other assessments	Comparisons between the Group 2 and 3 and the different delivery models will analyse whether the 'supported inclisiran' arm generates greater benefits than the injection only model in terms of outcomes other than LDL cholesterol: patient adherence, acceptability (both through PROMs) and wider cardiovascular risk. A process evaluation will build on and extend the study results, providing in-depth data on adherence and acceptability (through detailed interviews) with patients and professionals involved in the trial.
Data analysis	The primary effectiveness objective of this study is to demonstrate superiority of each inclisiran arm compared to standard of care + behavioural support in terms of the percentage change from baseline in LDL-C to Day 270 in adults with elevated LDL-C. The statistical hypotheses that will be tested for each inclisiran arm are as follows: • H0: The difference between participants treated with inclisiran (+/- behavioural support) and standard of care + behavioural support in the least squares mean percentage change from baseline to the Day 270 visit in LDL-C= 0 • Ha: The difference between participants treated with inclisiran (+/- behavioural support) and standard of care + behavioural support in the least squares mean percentage change from baseline to the Day 270 visit in LDL-C < 0 The primary endpoint will be analysed using an analysis of covariance model (ANCOVA) with imputation for missing data performed using the washout model as discussed in Section 12.4.2. The difference in least squares means between treatment groups and corresponding 2-sided 95% confidence intervals will be reported. The Full Analysis Set (FAS) will be used for this analysis. Full details on the model and imputation will be provided in the SAP.

	The process evaluation will be conducted and analysed using the Consolidated Framework for Implementation Research (CFIR).
Key words	implementation, preference, utility, process evaluation, inclisiran, Atherosclerotic Cardiovascular Disease, ASCVD, ASCVD-risk equivalents, Cholesterol, LDL-C, primary care

1 Introduction

1.1 Background

1.1.1 Cardiovascular benefits of lowering LDL cholesterol

Elevated low-density lipoprotein associated cholesterol (LDL-C), is one of the major risk factors for coronary heart disease (CHD) (Grundy et al, 2004). Despite advances in treatment, atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death and disability worldwide and is expected to remain so beyond 2040 (Foreman et al, 2018). After 30 years of progress, death rates associated with ASCVD may be increasing in the United States once more (Benjamin et al, 2019).

Multiple factors contribute to the development of ASCVD. However, strong and consistent evidence from genetics, epidemiology, and randomised trials, establishes that among these factors, LDL-C is not merely a biomarker of increased risk, but a causal and modifiable factor in ASCVD (Ference et al, 2017).

Large outcome trials have consistently confirmed the benefit of cholesterol lowering therapy (statins). In the largest study, the Heart Protection Study, 20,536 subjects were treated with simvastatin for five years. The study was large enough to allow multiple subgroup analyses. These showed that the reduction in relative risk was similar even when subjects had risk factors including diabetes, hypertension, and smoking (Goldstein, 2015). A recent meta-analysis of 22 statin trials involving 134,000 participants concluded that for each reduction of LDL-C of 1 mmol/l (40 mg/dl) cardiovascular events are reduced by 20%, even in people who were considered to be at low risk (Cholesterol Treatment Trialists, 2012). These findings have made statin the cornerstone of clinical practice.

Despite the proven efficacy of statins, there is still a considerable variability in individuals to these drugs, even when being treated with a high intensity regime (Ridker, 2016). Furthermore, not all people tolerate statins or are able to take statins at sufficient intensive doses, and some observational studies have demonstrated as many as half of individuals who begin statin therapy discontinue it within 12 months (Zang, 2013).

Therefore, there is a clear unmet medical need for additional options beyond current available treatments for the lowering of LDL-C.

1.1.2 Inhibition of PCSK9 as a therapeutic target

LDL Receptors (LDLR) on the surface of liver cells are a key determinant of circulating levels of LDL-C (Goldstein and Brown, 2009). Proprotein convertase subtilisin/kexin type 9 (PCSK9) is an enzyme mainly of hepatic origin that circulates in the blood and binds to the LDLR (Seidah, 2014). The PCSK9-LDLR complex is then degraded by lysosomes in the liver cells and circulation of LDLR to the surface of the liver cells is reduced. As a consequence, the number of LDL receptors on liver cells is reduced and there is reduced uptake of LDL-C from the blood (Horton et al, 2007). Lower levels of circulating PCSK9 lead to higher hepatic LDLR expression and lower circulating LDL-C levels.

Gain of function mutations in the PCSK9 gene result in familial hypercholesterolaemia and increased rates of coronary events. By contrast, loss of function mutations are associated with

reductions in LDL-C levels and lower risk of coronary events. From a safety perspective, individuals with no circulating PCSK9 due to compound heterozygous loss of function mutations in PCSK9 do not appear to have any obvious clinical disadvantages (Zhao, 2006). Mechanistic studies of PCSK9 have identified PCSK9 as playing a key role in controlling the levels of LDLR on the surface of hepatocytes. PCSK9 is responsible for degrading LDLR and prevents recycling to the cell surface where it removes LDL-C from the plasma. Therapeutic strategies designed to reduce circulating PCSK9 include binding it in the circulation with monoclonal antibodies or modified binding proteins and reducing production of it in the liver with small interfering RNAs (siRNAs).

Clinical studies with PCSK9 blocking antibodies have demonstrated significant effects on lowering LDL-C in healthy volunteers and in subjects with hypercholesterolemia with and without statins (Banerjee, 2012, Dias et al, 2012, Milazzo, 2012, Raal et al 2012). In addition, recent clinical studies indicate that statin treatment increases PCSK9 levels and as a result, may limit statin effectiveness as the dose is increased (Careskey et al, 2008; Davignon and Dubuc, 2009; Welder et al, 2010). Collectively these studies support the hypothesis that lowering of circulating plasma PCSK9 by inhibiting the synthesis of PCSK9 protein in hepatocytes should lower LDL-C, potentially resulting in reduced risk of CHD.

1.1.3 Inhibition of PCSK9 with siRNA has potential advantages over antibodies

Ribonucleic acid interference (RNAi) is a naturally occurring cellular mechanism mediated by small interfering RNAs (siRNAs) for regulating gene expression. Inclisiran is a chemically synthesised siRNA, covalently linked to a ligand containing three N-acetylgalactosamine (GalNAc) residues. These GalNAc residues bind to abundant liver-expressed asialoglycoprotein receptor (ASGPR), leading to inclisiran uptake specifically into hepatocytes. When introduced into the hepatocyte, inclisiran engages the natural pathway of RNA interference (RNAi) by binding intracellularly to the RNA-induced silencing complex (RISC), enabling it to cleave mRNA molecules encoding PCSK9 specifically. The cleaved PCSK9 mRNA is degraded and thus unavailable for protein translation, which results in decreased levels of the PCSK9 protein. A single siRNA-bound RISC is catalytic and cleaves many mRNA transcripts and the duration of action is anticipated to be longer than other mechanisms. A key potential advantage of inclisiran's mechanism of action is that the duration of its effect is longer than that of monoclonal antibodies to PCSK9.

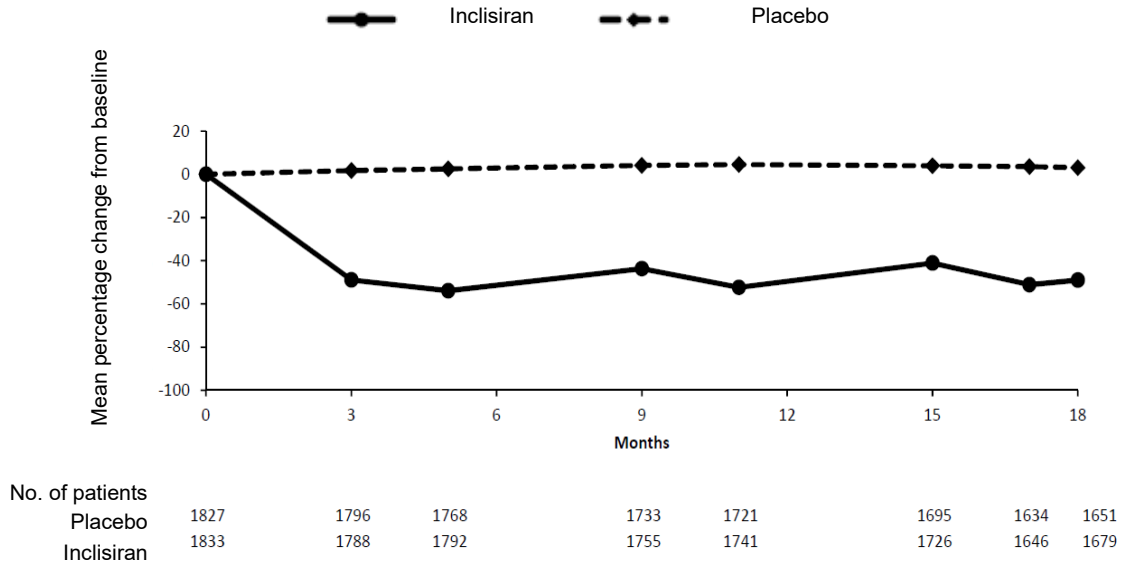
1.1.4 Clinical efficacy and safety

The efficacy of inclisiran was evaluated in three phase III studies in patients with ASCVD or ASCVD risk equivalents (type 2 diabetes mellitus, familial hypercholesterolaemia, or 10-year risk of 20% or greater of having a cardiovascular event assessed by Framingham Risk Score or equivalent) and/or familial hypercholesterolaemia (FH). Patients were taking a maximally tolerated dose of statin with or without other lipid-modifying therapy and required additional LDL-C reduction (patients unable to reach their treatment goals). Approximately 17% of patients were statin intolerant. Patients were administered subcutaneous injections of 284 mg inclisiran or placebo on day 1, day 90, day 270 and day 450. Patients were followed until day

540. The effect of inclisiran on cardiovascular morbidity and mortality has not yet been determined.

In the phase III pooled analysis, subcutaneously administered inclisiran lowered LDL-C between 50% and 55% as early as day 90 (Figure 1-1), which was maintained during long-term therapy. Maximal LDL-C reduction was achieved at day 150 following a second administration. Small but statistically significant increased LDL-C reductions up to 65% were associated with lower baseline LDL-C levels (approximately <2 mmol/l [77 mg/dl]), higher baseline PCSK9 levels and higher statin doses and statin intensity.

Figure 1-1 Mean percentage change from baseline LDL-C in patients with primary hypercholesterolaemia and mixed dyslipidaemia treated with inclisiran compared to placebo (pooled analysis)



To date, injection site reaction is the only adverse drug reaction that has been identified for inclisiran. None of the reported injection site reactions were considered to be serious.

In Phase II study MDCO-PCS-15-01 (ORION-1), clinically relevant injection site reactions were reported in a total of 13 (3.5%) inclisiran-treated subjects and no subjects (0.0%) in the placebo group following a single dose (single and double dose groups combined) through Day 90. Injection site reactions were reported in a total of 6 (3.4%) inclisiran-treated subjects and no subjects (0.0%) in the placebo group following a second dose. No observed difference or dose relationship was observed between inclisiran groups. The frequency of injection site reactions was similar after a second dose of inclisiran (3.4%) to that observed after the first dose (3.5%). All AEs at the injection site resolved without sequelae with the exception of one subject who received a single dose of inclisiran sodium 300 mg on Day 1 and continued to have a 2 mm erythema spot at the injection site on Day 210.

In the Phase III studies MDCO-PCS-17-03 (ORION-9), MDCO-PCS-17-04 (ORION-10) and MDCO-PCS-17-08 (ORION-11), more inclisiran-treated subjects, 8.2% (150/1833), reported at least one Treatment Emerged Adverse Events (TEAE) at the injection site than placebo-treated subjects 1.8% (33/1822). Of the 183 subjects with a TEAEs at the injection site, the majority had a mild event (4.2%; 154/3655 subjects) and none had a severe event. No inclisiran-treated subject had a serious TEAE at the injection site. Four (4) inclisiran-treated subjects withdrew from study drug due to non-serious TEAEs at the injection site.

From the reported TEAEs at the injection site, more inclisiran-treated subjects (5.0%; 91/1833) reported clinically relevant TEAEs at the injection site (preferred terms of injection site erythema, injection site hypersensitivity, injection site pruritus, injection site rash, and injection site reaction) than placebo-treated subjects (0.7%; 12/1822). Clinically relevant TEAEs at the injection site were reported for inclisiran-treated subjects as follows: injection site erythema (37 events in 30 subjects), injection site hypersensitivity (3 event in 2 subjects), injection site pruritus (9 events in 8 subjects), injection site rash (20 events in 13 subjects), and injection site reaction (84 events in 56 subjects). The time to first clinically relevant TEAEs at the injection site was usually observed more than 12 hours after the time of injection and this was similar for those that were clinically relevant. The TEAE at the injection site were generally transient.

1.1.4.1 ASCVD and ASCVD risk equivalents

Two studies were conducted in patients with ASCVD and ASCVD risk equivalents (ORION-10 and ORION-11). Patients were taking a maximally tolerated dose of statins with or without other lipid-modifying therapy, such as ezetimibe, and required additional LDL-C reduction. As lowering LDL-C is expected to improve cardiovascular outcomes, the co-primary endpoints in each study were the percentage change in LDL-C from baseline to day 510 relative to placebo and the time-adjusted percentage change in LDL-C from baseline after day 90 and up to day 540 to estimate the integrated effect on LDL-C over time.

ORION-10 was a multicentre, double-blind, randomised, placebo-controlled 18-month study conducted in 1,561 patients with ASCVD. The mean age at baseline was 66 years (range: 35 to 90 years), 60% were ≥65 years old, 31% were women, 86% were White, 13% were Black, 1% were Asian and 14% were Hispanic or Latino ethnicity. The mean baseline LDL C was 2.7 mmol/l (105 mg/dl). Sixty-nine percent (69%) were taking high-intensity statins, 19% were taking medium-intensity statins, 1% were taking low-intensity statins and 11% were not on a statin. The most commonly administered statins were atorvastatin and rosuvastatin.

Inclisiran significantly reduced the mean percentage change in LDL-C from baseline to day 510 compared to placebo by 52% (95% CI: -56%, -49%; p <0.0001).Inclisiran also significantly reduced the time-adjusted percentage change in LDL-C from baseline after day 90 and up to day 540 by 54% compared to placebo (95% CI: -56%, -51%; p <0.0001). At day 510, the LDL-C target of <1.8 mmol/l (70 mg/dl) was achieved by 84% of inclisiran patients with ASCVD compared to 18% of placebo patients.

Consistent and statistically significant (p<0.0001) reductions in percentage change in LDL-C from baseline to day 510 and time-adjusted percentage change in LDL-C from baseline after day 90 and up to day 540 were observed across all subgroups irrespective of baseline

demographics, baseline disease characteristics (including gender, age, body mass index, race and baseline statin use), comorbidities and geographic regions.

ORION-11 was an international, multicentre, double-blind, randomised, placebo-controlled 18-month study which evaluated 1,617 patients with ASCVD or ASCVD risk equivalents. More than 75% of patients were receiving a high-intensity statin background treatment, 87% of patients had ASCVD and 13% were ASCVD risk equivalent. The mean age at baseline was 65 years (range: 20 to 88 years), 55% were ≥65 years old, 28% were women, 98% were White, 1% were Black ,1% were Asian and 1% were Hispanic or Latino ethnicity. The mean baseline LDL-C was 2.7 mmol/l (105 mg/dl). Seventy-eight percent (78%) were taking high-intensity statins, 16% were taking medium-intensity statins, 0.4% were taking low-intensity statins and 5% were not on a statin. The most commonly administered statins were atorvastatin and rosuvastatin.

Inclisiran significantly reduced the mean percentage change in LDL-C from baseline to day 510 compared to placebo by 50% (95% CI: -53%, -47%; p<0.0001). Inclisiran also significantly reduced time-adjusted percentage change in LDL-C from baseline after day 90 and up to day 540 by 49% compared to placebo (95% CI: -52%, -48%; p<0.0001).

At day 510, the LDL-C target of <1.8 mmol/l (70 mg/dl) was achieved by 82% of inclisiran patients with ASCVD compared to 16% of placebo patients. In patients with an ASCVD risk equivalent, the LDL-C target of <2.6 mmol/l (100 mg/dl) was achieved by 78% of inclisiran patients compared to 31% of placebo patients.

Consistent and statistically significant (p<0.05) percentage change in LDL-C from baseline to day 510 and time-adjusted percentage change in LDL-C from baseline after day 90 and up to day 540 was observed across all subgroups irrespective of baseline demographics, baseline disease characteristics (including gender, age, body mass index, race and baseline statin use), comorbidities, and geographic regions.

1.1.4.2 Heterozygous familial hypercholesterolaemia

ORION-9 was an international, multicentre, double-blind, randomised, placebo-controlled 18-month trial in 482 patients with heterozygous familial hypercholesterolaemia (HeFH). All patients were taking maximally tolerated doses of statins with or without other lipid-modifying therapy, such as ezetimibe, and required additional LDL-C reduction. The diagnosis of HeFH was made either by genotyping or clinical criteria (“definite FH” using either the Simon Broome or WHO/Dutch Lipid Network criteria).

The co-primary endpoints were the percentage change in LDL-C from baseline to day 510 relative to placebo, and the time-adjusted percentage change in LDL-C from baseline after day 90 and up to day 540 to estimate the integrated effect on LDL-C over time. Key secondary endpoints were the absolute change in LDL-C from baseline to day 510, the time-adjusted absolute change in LDL-C from baseline after day 90 and up to day 540 and the percentage change from baseline to day 510 in PCSK9, total cholesterol, Apo-B, and non-HDL-C. Additional secondary endpoints included the, individual responsiveness to inclisiran and the proportion of patients attaining global lipid targets for their level of ASCVD risk. The mean age at baseline was 55 years (range: 21 to 80 years), 22% were ≥65 years old, 53% were women, 94% were White, 3% were Black, 3% were Asian and 3% were Hispanic or Latino

ethnicity. The mean baseline LDL-C was 4.0 mmol/l (153 mg/dl). Seventy-four percent (74%) were taking high-intensity statins, 15% were taking medium-intensity statins and 10% were not on a statin. Fifty-two percent (52%) of patients were treated with ezetimibe. The most commonly administered statins were atorvastatin and rosuvastatin.

Inclisiran significantly reduced the mean percentage change in LDL-C from baseline to day 510 compared to placebo by 48% (95% CI: -54%, -42%; p<0.0001).Inclisiran also significantly reduced the time-adjusted percentage change in LDL-C from baseline after day 90 and up to day 540 by 44% compared to placebo (95% CI: -48%, -40%; p<0.0001).

At day 510, 52.5% of inclisiran patients with ASCVD achieved their LDL-C target of <1.8 mmol/l (70 mg/dl) compared to 1.4% of placebo patients with ASCVD, while in the group with ASCVD risk equivalents 66.9% of inclisiran patients achieved their LDL-C target of <2.6 mmol/l (100 mg/dl) compared to 8.9% of placebo patients. Consistent and statistically significant (p<0.05) percentage change in LDL-C from baseline to day 510 and time-adjusted percentage change in LDL-C from baseline after day 90 and up to day 540 were observed across all subgroups irrespective of baseline demographics, baseline disease characteristics (including gender, age, body mass index, race and baseline statin use), comorbidities, and geographic regions.

1.1.5 Background to the research framework

There is evidence to show that real-world adherence with lipid lowering therapies is suboptimal (Akyea et al., 2019). The phase III clinical development programme summarised in Section 1.1.4 demonstrates the effective LDL-C reduction profile of inclisiran. In addition, the dosing regimen of 6-monthly maintenance injections provides a delivery method which may help to improve adherence to lipid lowering therapies with minimal impact on [redacted]

The potential to address large population health burdens, such as cardiovascular disease, is greater in integrated healthcare systems that are able to support innovation. This requires understanding how a new technology such as inclisiran could be deployed and delivered into a system of care in such a manner that it would be possible to treat the appropriate patients at a population-health level.

The UK National Health Service (NHS) presents an ideal framework within which to consider population health approaches for the implementation of new health technologies. This is due to the primary care focused management of patients with chronic conditions, the increasing robustness of electronic medical records (EMR), clear and aligned commissioning processes and goals within the NHS Long-Term plan regarding the optimisation of service delivery to patients within their locality.

Within the NHS, the Greater Manchester Health and Social Care partnership - a geographical region covering in excess of 2 million patients – presents an ideal test-bed opportunity to research the implementation of inclisiran with a population health approach utilising a primary care model of delivery. This is due to the cohesion of the primary and secondary care EMR in Greater Manchester, their established use of implementation science approaches to assess new interventions and their established primary care networks.

The implementation research study described in this protocol is designed to provide and assess evidence for the implementation of inclisiran within a primary care setting in the NHS. The protocol describes an established implementation science approach utilising a Type 1 hybrid design described in subsequent sections.

2 Purpose and rationale

The purpose of this study is to evaluate the implementation of inclisiran in a regional primary care setting in the UK.

Using implementation science methodology, the study seeks to assess the effect of 9 months treatment with inclisiran +/- behavioural support, compared to standard of care + behavioural support, on LDL-C reduction, [redacted] assessments of patient and healthcare professional (HCP) satisfaction, [redacted] and healthcare service process evaluation.

3 Objectives

3.1 Primary Objective

The primary objective of this study is to demonstrate superiority of inclisiran +/- behavioural support compared to standard of care + behavioural support in a primary care setting, in terms of the percentage change in LDL-C from baseline to Day 270 in adults with elevated LDL-C.

3.2 Secondary Objectives

The secondary objectives of this study are to evaluate the implementation of inclisiran +/- behavioural support compared to standard of care + behavioural support in a primary care setting using the following assessments:

- Measures of patient satisfaction using the validated CSQ-8 (Client Satisfaction Questionnaire) administered after treatment at day 90.
- Measures of patient activation and empowerment using the validated Patient Activation Measure (PAM) questionnaire administered after treatment at day 90.
- Measures of adherence to cardiovascular disease self-management using the validated Patient Activation Measure (PAM) questionnaire administered after treatment at day 90 and using assessment of medication adherence during the study period.
- A process evaluation conducted using the Consolidated Framework for Implementation Research (CFIR) which will explore inclisiran delivery at three levels:
  - Feasibility and acceptability of delivery models for inclisiran to patients
  - Feasibility and acceptability of delivery models for inclisiran to providers (inner setting)
  - Wider ‘transactability’ of the proposed delivery models (outer setting)
  - The service costs of each delivery model
  - The acceptability and perceived sustainability of patient identification and referral routes

- Serious adverse event profile and adverse events leading to treatment discontinuation

3.3 [redacted]

[redacted]

4 Study design

This study is an implementation research study that utilises implementation science methodology and use of the electronic medical record (EMR).

The study is based on the following principles:

- It is run in the setting where inclisiran is intended to be implemented in clinical practice, with the intention of understanding the effects of innovations within the real world conditions of everyday clinical practice
- Inclusion / exclusion criteria reflect the proposed license, with the intention of working with populations that will be affected by an intervention, rather than selecting patients who are suitable for a standard clinical trial.
- Health delivery context: taking account institutional and health system contexts – including the viewpoints of various stakeholder including commissioners, system managers and clinicians.

The primary focus of this study is implementation and 'transactability' – how to organise, deliver and maintain an innovative treatment for ASCVD in a primary care setting in a sustainable way.

4.1 Overview of Implementation Science

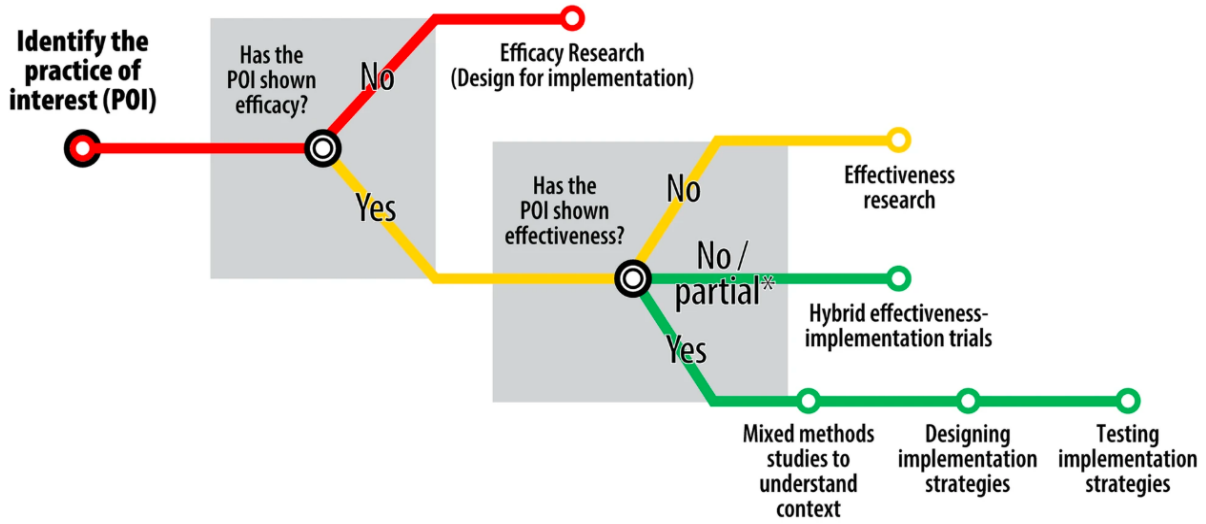
Implementation Science is the scientific study of methods to promote the systematic uptake of proven clinical treatments, practices, organisational, and management interventions into routine practice, and hence to improve health (Eccles et al, 2006). This also encompasses the study of influences on patient, professional, and organisational behaviours in healthcare systems.

The field is largely focused on interventions which have established effectiveness in the healthcare (non-trial) environment, after marketing-authorisation. It is unusual to encounter implementation science in trials of interventions ahead of marketing authorisation. However, increasingly, implementation science methods are employed in pragmatic effectiveness studies

in order to provide a route to appropriately accelerated deployment and more rapid patient benefit. This type of approach is key to understanding how and why innovations are successfully implemented in some settings but not others and is increasingly necessary to provide evidence for patient access to new technologies. This need to gather data to inform implementation efforts has become a mainstay of guidance for pragmatic evaluations (Moore, 2015).

This study is best conceptualised as a *hybrid design* (Pinnock et al, 2017). Hybrid designs have emerged from wider concerns relating to the need to speed up the transfer of clinical research findings into routine practice. In an effectiveness-implementation hybrid design there is a dual focus a priori in assessing clinical effectiveness in the appropriate setting and implementation (see Figure 4-1).

Figure 4-1 Types of research design (adapted from Lane-Fall et al, 2019)



This study is a type 1 hybrid design where the focus is on testing a clinical intervention in the appropriate real-world situation (in this case primary care) while observing and gathering information on its 'implementability'. The interventional aspect of the study will be categorised as a phase IIIb, multicentre, open-label, randomised controlled study in 900 participants on established lipid lowering medication or, have been recommended lipid lowering therapy by their healthcare provider but are unable to tolerate treatment.

Type 1 hybrid designs sit at the boundaries of implementation science and are used to identify what is needed to support implementation in the real world - exploring the resources, behaviours and practices that can act as 'barriers' or 'enablers' to the implementation of a given intervention. Gathering this information on the active components and optimal model of service delivery is the crucial first step of planning to scale to spread the delivery of an intervention more widely in the appropriate patient population.

The phase III ORION clinical development program demonstrated the safety and efficacy of inclisiran in the clinical trial setting (Section 1.1.4). However, it is acknowledged that

randomised clinical trials by definition are highly controlled and enroll a more selected patient population than is expected to be prescribed the medication post-approval. [redacted]

A Type 1 hybrid design intends to minimise the burden of the trial on participants and healthcare providers whilst mimicking the real-world delivery of healthcare as closely as possible. The Salford Lung Study (Vestbo, 2016) was the first pre-registration pragmatic trial, achieved using bespoke technology developed by NWEH (New, 2014) designed to achieve these aims. This approach integrated primary and secondary care Electronic Medical Record (EMR) systems from hospitals and surrounding primary care practices in real time, allowing HCP to identify patients, assess outcomes, and collect real life setting data without direct contact with patients, in addition to providing safety surveillance by remote monitoring (Collier, 2016).

4.2 The structure of this study and use of the EMR

This study will be conducted using NWEH's ConneXon trials platform which integrates patient level electronic healthcare record data from primary care and secondary care via national data sources, to support the integration of 'real-world evidence' from individually consented participants. The majority of data will be directly extracted from the patient EMR in order to minimise direct participant contact and maximise the outcomes of interest related to implementation. Some study specific data not routinely collected will also be reported by the investigator or delegate in an integrated Electronic Case report Form (eCRF) for accuracy and in compliance with regulatory standards.

The study can therefore be divided into three main elements:

- A prospective phase IIIb intervention with inclisiran +/- behavioural support compared to standard of care + behavioural support in a type 1 hybrid implementation design in a primary care population.

D [redacted]

- A process evaluation that will ascertain the views of patients and healthcare providers about the service they have received or provided and its potential transactability across the NHS.

The population of interest is adult participants on established lipid lowering medication or, have been recommended lipid lowering therapy by their healthcare provider but are unable to tolerate treatment. Based on the statistical power calculation (see Section 12.8) 900 participants (300 per treatment group) at up to 30 primary care centres will be recruited.

4.3 The Process Evaluation Sub-Study

The primary focus of the VICTORION-Spirit study is implementation and 'transactability' – how to organise, deliver and maintain an innovative treatment for secondary prevention in a

primary care setting in a sustainable way. This information will be used to inform future implementation efforts in the NHS and beyond.

Understanding how and why healthcare innovations are successfully implemented in some settings but not others is a key issue in supporting appropriate broader uptake and access to innovative medicines. The role of process evaluation is to shed light on the structures, resources and processes through which successful delivery can be achieved. We will explore how inclisiran may be implemented into routine care pathways using approaches that are feasible and acceptable both to patients and to those providing the services.

To identify what is needed to support the implementation of inclisiran in the real world, we will draw upon a framework known as the Consolidated Framework for Implementation Research (CFIR) (Damschroder 2009). Grounded in Diffusion of Innovations theory, CFIR is widely used in implementation research to guide systematic assessment factors that influence intervention implementation and effectiveness (Kirk 2016). The framework comprises a comprehensive taxonomy of 39 operationally defined constructs across five domains that are likely to influence the implementation of complex interventions. These are:

1. Intervention characteristics – are there features of the intervention might influence implementation (in this case inclisiran itself and/or the delivery mode)
2. Inner setting – how do the ways that general practices organise care delivery influence implementation
3. Outer setting – are there wider contextual or policy factors that might influence implementation and sustainability
4. The characteristics of individuals involved in implementation
5. How the process of implementation is actually enacted

Each of these five domains is further divided into constructs that have been associated with effective implementation (for detailed descriptions of each construct see: http://www.cfirguide.org/). We selected the CFIR as our guiding framework because it provides a standardised structure for aggregating findings in a systematic manner. Using CFIR we will explore inclisiran delivery at three levels:

1. Feasibility and acceptability of delivery models for inclisiran to patients
2. Feasibility and acceptability of delivery models for inclisiran to providers (inner setting)
3. Wider 'transactability' of the proposed delivery models (outer setting)

4.3.1 Level 1: Feasibility and acceptability of delivery models for inclisiran to patients

4.3.1.1 Design and setting

We will conduct semi-structured telephone interviews with patients to understand the feasibility and acceptability of each delivery models for inclisiran.

4.3.1.2 Sampling and recruitment

Purposive sampling techniques will be used to recruit respondents to assess how the different delivery modes are experienced. We expect to conduct a minimum of 30 interviews in this phase. This sample should allow some scope to examine how adherence, acceptability and

experience varies across different demographic groups and ensure diversity in relation to individual variables such as age, gender, ethnicity and deprivation. The final sample size will be contingent on iterative analysis and saturation of themes.

4.3.1.3 Data collection

Telephone interviews will be arranged at a day/time suitable for the respondent. We will use topic guides informed by CSQ and PAM to understand patients' interactions with and experience of each delivery model. Interviews will cover access and ask how acceptable patients found both the injection and the processes of care delivery. As data collection progresses, the topic guide will be iteratively reviewed to incorporate issues not previously included, but which are relevant to the study. With the respondents' permission, telephone interviews will be digitally audio-recorded on a university provided encrypted audio device. The researcher will write field notes (immediately following a telephone interview) to provide context to the transcribed interview data.

4.3.1.4 Analysis

Interviews will be audio-recorded with consent, transcribed and thematically analysed using a modified framework approach and using NVivo software to manage the data. This produces a matrix of summarised data providing a structure for analysis and interpretation (Gale 2013). This approach will allow us to: (a) answer the specific research questions we have set, whilst (b) allowing important insights to be produced inductively. The use of a modified framework approach will also utilise the strengths of Framework analysis in providing structure to the analysis of large datasets, especially allowing comparisons between different participant groups on key issues. As per (Gale 2013), we also intend to engage the wider research team in the analysis process.

4.3.2 Level 2: Feasibility and acceptability of delivery models for inclisiran to providers

4.3.2.1 Design and setting

We will conduct telephone interviews with providers (Practice Managers, GPs, Pharmacists, Practice Nurses, etc.) to explore the implementation of each delivery model in primary care and understand the structures, resources and processes required to deliver inclisiran as part of routine practice.

4.3.2.2 Sampling and recruitment

We will aim to conduct semi-structured telephone interviews with a purposive sample of practice nurses, pharmacists, GPs and practice managers drawn from across all the proposed delivery models. We expect to conduct up to 50 interviews in this phase. We will sample across participating sites to ensure maximum variance in practice type and geographical area.

4.3.2.3 Data collection

Telephone interviews will be arranged for a time/day to suit the respondent. Interview topic guides will be informed by CFIR and will focus on the barriers and enablers to integrating

inclisiran delivery within existing practice routines. Specifically, we will focus on understanding:

- Stakeholders' perceptions about the relative advantage of the inclisiran and intervention complexity;
- How each delivery model is understood and compares with existing practices;
- How each delivery model is locally adapted and translated into practice;
- The acceptability and perceived sustainability of patient identification and referral routes;
- Assessing barriers and enablers (and any unintended consequences) to implementation.

As with patient interviews, the topic guide will be iteratively reviewed to incorporate issues not previously included, but which are relevant to the study. With the respondents' permission, telephone interviews will be digitally audio-recorded on a university provided encrypted audio device. The researcher will write field notes (immediately following a telephone interview) to provide context to the transcribed interview data.

4.3.2.4 Analysis

Interviews will be audio-recorded with consent, transcribed and thematically analysed using a modified framework approach and using NVivo software to manage the data. By 'modified' we mean that we will initially use the Framework approach to take an inductive approach to theme generation. Subsequent theme refinement will be deductive and guided by CFIR. This will enable us to produce a matrix of summarised data providing a structure for analysis. The overarching implementation analysis will then explore professional perceptions and attitudes towards inclisiran and each model of delivery; consider initial and enduring challenges as well as any unintended consequences arising from implementation. The analysis will then consider their wider 'transactability' of each delivery model namely the active ingredients in the form of structures, resources and processes required to enable successful delivery elsewhere.

4.3.3 Level 3: Exploring wider system readiness for inclisiran

4.3.3.1 Design and setting

We will conduct telephone interviews with NHS commissioners and regional and national policy makers to explore the wider 'transactability' of the proposed delivery models for inclisiran beyond the auspices of the trial setting.

4.3.3.2 Sampling and recruitment

A mix of purposive and snowball sampling techniques will be used to recruit respondents. We expect to conduct a minimum of 10 interviews in this phase. We anticipate that interviews will include NHS commissioners, and representatives from the Academic Health Science Network, NHS England and the NHS Accelerated Access Collaborative. We will work with Health Innovation Manchester to identify potential targets for interview. Once identified, we will send potential respondents an email inviting them to take part in an interview (with the participant information sheet attached). Reminder emails will be sent to non-responders. Snowball recruitment may be employed if additional names are provided by participants.

4.3.3.3 Data collection

Telephone interviews will be arranged for a time/day to suit the respondent. Interview topic guides will again be informed by CFIR and will explore the strategic vision for innovation uptake in the NHS generally and views on and preferences for the delivery models to be implemented specifically. In doing so, interviewees will be asked to consider issues relating the wider 'transactability' of the proposed delivery models for inclisiran beyond the auspices of the trial setting. This will include necessary structures, resources and processes as well as preferred forms of reimbursement.

4.3.3.4 Data analysis

Initial analysis will follow a similar approach to the provider interviews above from which a blueprint of how to implement inclisiran more widely will be generated. This blueprint will combine data from all three levels of inquiry with implementation costs and outcomes to identify the 'core enabling ingredients' and preferred model of service delivery deemed necessary to support the uptake of inclisiran across the NHS.

Implementation costs will be largely made up of the time and resources required to deliver each inclisiran model. The costs of health professional input will be based on national average rates using PSSRU (Personal Social Services Research Unit) estimates (https://www.pssru.ac.uk/project-pages/unit-costs/). The length of each clinical encounter will be collected and coded to each practice, and costed on the basis of the full economic costs of the staff involved. Estimates of the additional time required from the general practice staff will be obtained. These unit costs will then be multiplied by the time spent recorded in the call log or timesheet during the trial period to estimate the costs of delivering each model. The data will be used to construct models of the potential implementation costs from a Clinical Commissioning Group perspective and how these costs may vary with different levels of implementation.

4.3.4 Standards of reporting

We will adhere to recommendations of the EQUATOR Network (Enhancing the QUAlity and Transparency Of health Research) for transparent and accurate reporting and wider use of health research. The standards for reporting qualitative research (SRQR) guidance will be used to ensure rigorous reporting of the process evaluation.

Without sufficient detail, it can be difficult for other interested parties to determine what was actually implemented and/or for others to use or replicate the intervention in other studies or settings. We will ensure the quality of intervention description for each delivery model through use of the Template for Intervention Description and Replication (TIDieR) checklist.

4.4 Patient identification and recruitment process

4.4.1 Cohort finding solutions

In addition to lipid profile and implementation outcomes, this trial also seeks to inform NHS England (NHS-E) on appropriate patient identification strategies that may be used to identify and treat the estimated 300,000 patients in England with established ASCVD and LDL-C

>2.6mmol/L that could benefit from treatment with inclisiran. It is anticipated that this delivery will be in primary care via GPs but working in collaboration with other HCPs. Therefore, patient identification and recruitment processes are an important component of the study design.

The challenges to identifying this patient population are:

- **Consistency of query generation**

GP systems have the capability to create queries based on coded information within the system. There are four GP system suppliers in the UK. Queries can be generated at system wide level but are more commonly done at a local / federation level. There is no guarantee of consistency.

- **Incomplete coded data at GP level**

Work previously conducted between NWEH and The Medicines Company (MDCO) demonstrated that a significant number of events for patients with ASCVD which occurred in secondary care were not coded in primary care.

- **Identifying the intervention resistant population**

Understanding how to access and engage with those patients who resist intervention and are likely to be the most in need of a cholesterol lowering medication, and gain the greatest benefit.

4.4.2 Patient identification in this study

The study will be conducted in primary care centres across Greater Manchester with a network of research ready GPs. Eligibility and recruitment to the study will be optimised by using NWEH's proven Feasibility Assessment and Recruitment System for Improving Trial Efficiency (FARSITE) for identification and recruitment at participating GP practices (see Section 8.2).

FARSITE uses coded GP data to create a single query run across participating practices over a de-identified data set. Using the primary care data set and outcomes from initial recruitment phases as 'training data', NWEH will apply its machine learning tools to understand how the recruitment can be refined by modelling for missing data around secondary care events. This modelling will look at data beyond the clinically coded data directly related to ASCVD and will include other comorbidities and social determinants as recorded in GP data.

FARSITE will be used to identify the most suitable GP practices within Greater Manchester by ascertaining the maximum number of patients from up to 30 GP practices that meet the inclusion criteria. Once the list of potential patients per practice has been identified, the GP will review the patient's medical records manually to confirm eligibility for the study against the inclusion / exclusion criteria (Section 5.1).

There may be occasions for individual GP practices to use their local electronic health record (EHR) to run local searches to identify eligible participants. Such use of EHR searches would only be in exceptional circumstances as part of business contingency planning to minimise impact of a slower than expected recruitment rate on study delivery.

In the event of a global health disruption event, such as a pandemic/epidemic (e.g. COVID-19), that limits or restricts access to Greater Manchester primary care centres, there may be occasion that primary care centres are identified which are located in the surrounding geographical area of Greater Manchester, however this would only be in exceptional circumstances.

Following their review of the list of potential patients, the GP will write to eligible patients inviting their participation in the study using the REC approved invitation letter and brief patient information sheet (PIS). This process of inviting potential participants will optimised using the FARSITE Recruitment tool. The invitation letter will give clear instructions as to the study requirements, as well as the details of the study team so that interested patients can easily contact the appropriate person directly if they wish to participate in the study. Once the invitation letter and brief PIS have been sent out to the patient, a follow-up telephone call from either the patient's GP or delegate will be completed to confirm receipt and establish the patients' interest in the study. Patients which express an interest will be sent the full PIS and invited to attend a screening visit.

4.5 Treatment groups and outcome assessments

Participants will be required to attend at least three study visits, including a baseline/screening visit, a Day 90 visit and an end of study visit (EOS) during the study period. Participants randomised to Group 1 do not need to attend the Day 1 visit but can receive a phone call instead.

Visits will be planned in accordance with the timings described in the Assessment Schedule (see Table 8-1)

At the baseline visit/screening on receipt of a signed consent form, eligible participants will be randomised to one of the three treatment groups:

- **Group 1:** Participants will continue to receive their background lipid lowering therapy (see Section 6.1.2 plus behavioural support (see Appendix 1)).
- **Group 2:** Participants will continue to receive their background lipid lowering therapy (see Section 6.1.2), plus inclisiran for injection (delivered in an injection-only model).
- **Group 3:** Participants will continue to receive their background lipid lowering therapy (see Section 6.1.2), plus inclisiran for injection (delivered in an injection-only model), plus behavioural support (see Appendix 1).

In order to confirm the efficacy findings from the phase III inclisiran studies in the primary care setting, Group 1 will form an enhanced control group. Participants in this group will continue to receive their background lipid lowering therapy optimised by monthly telephone based behavioural support programme delivered throughout the study period.

Participants randomised to Group 2 and Group 3 will be administered a single SC 300mg inclisiran injection at predefined time points described in the visit schedule and assessments (Section 8). The HCP who administers each dose of inclisiran for participants randomised to Group 2 and Group 3 will be decided by the GP PI at each site, in common with clinical practice within that primary care setting. Therefore, inclisiran may be administered by a GP, practice nurse, practice pharmacist or delivered and administered by a homecare team (Figure 4-2). Participants receiving inclisiran administered by a GP, practice nurse or practice pharmacist will be required to attend their GP practice or local Hub for administration of the study drug. The homecare team will administer inclisiran to participants in their own home setting. These visits will be performed by experienced HCPs with anaphylaxis training and following local guidelines and SOPs. This approach to recruitment is to enable participants who ordinarily may be unable to attend the GP practice due to a debilitating condition or travel burden to be involved

in the study. If a participant receives the study medication at home the lipid profile test at Day 90 will also be performed at home.

In the event of a global health disruption event, such as a pandemic/epidemic (e.g. COVID-19), that limits or prevents access to the GP practice, an alternative qualified research site already participating in the study may be used to conduct study activities per protocol.

All participants will receive a point of care blood test (see visit schedule in Section 8) to assess changes in lipid profile during the study.

All participants will be required to complete patient reported outcomes (PROMs) as part of the study. The CSQ-8 and PAM validated PROMs questionnaires and/or the [redacted] (Appendix 2[redacted]) will be provided to the study participant following their clinic visit. The participant is able to complete the questionnaire away from the clinical setting, thus providing the participant with sufficient space and time. Participant's refusal to complete all or any part of a PROM should be documented in the study data capture system and should not be captured as a protocol deviation.

The questionnaires will be returned to NWEH's research office in a stamped addressed envelope, for transcription into the eCRF. The questionnaires will be reviewed for completeness by the study team and participants contacted to ascertain any missing responses, the data will then be transcribed on to the eCRF. Unreturned questionnaires will be followed up twice at 2-weekly intervals.

Quantitative and qualitative methods (see Section 4.3) will be used to explore patient experience and adherence to the different models of care. [redacted] These will be based on existing validated PROMS questionnaires used for other conditions (see Appendix 4).

Any adverse events reported on a returned questionnaire will be assessed against the SAE reporting criteria for this study (Section 10) by the investigator or delegate and reported accordingly.

NWEH's ConneXon trials platform will be utilised for remote safety monitoring with minimal intervention, thereby reducing patient visits and maintaining real-world conditions for participants. Using this technology all [redacted] and serious adverse events (SAEs) will be alerted to the study team and reported to the sponsor within 24 hours of awareness.

4.5.1 Rationale for choice of background therapy

Participants taking part in this clinical study will continue to receive guideline recommended standard of care as background therapy (including statin therapy and/or other LDL-C lowering therapies).

4.5.2 Rationale for dose/regimen and duration of treatment

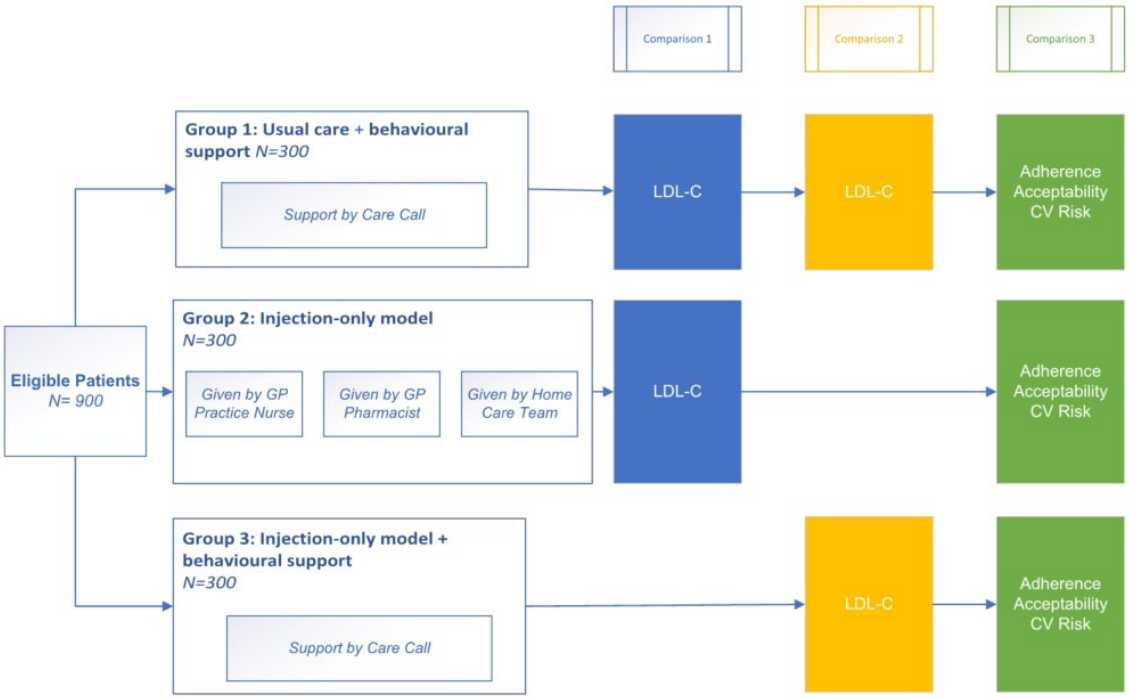
Previous studies have shown that a 300 mg dose of inclisiran sodium is well tolerated and provides maximum efficacy (i.e. doses higher than 300 mg did not provide additional efficacy in LDL-C lowering) (See Section 1.1.4). The 300 mg dose of inclisiran will be administered on Day 1 and Day 90. Modelling and simulation has demonstrated that this regimen will allow for

the necessary robust and sustained reduction in PCSK9 (and LDL-C) and has the potential to tackle the lack of adherence generally seen in the chronic management of subjects with hypercholesterolemia. The 300 mg dose of inclisiran will be used for the entire duration of this study for participants receiving inclisiran.

4.5.3 Rationale for choice of comparator arm

Inclisiran is expected to receive regulatory authority approval for use in addition to current standard of care for lipid management. Data from the UK healthcare environment shows that around 98% of patients with an LDL-C of >2.6mmol/L receive treatment with a statin as their standard of care. As lipid treatment should be accompanied by dietary and lifestyle advice, it was therefore appropriate for the comparator arm in this study to be standard of care for lipid management plus access to behavioural support.

Figure 4-2 Schematic of study design



4.6 Risks and benefits

Participants taking part in this study will continue to receive guideline recommended standard of care as background therapy (including statin therapy and/or other LDL-C lowering therapies) when administered inclisiran. Patients in this study will receive access to behavioural supportive care and/or inclisiran, and some degree of improved lipid management is expected in each treatment group. Reductions of LDL-C have been associated with reduced CV risk both by epidemiology and in controlled clinical trials (see Section 1.1.4).

To date, injection site reaction is the only adverse drug reaction that has been attributed to inclisiran treatment. None of the reported injection site reactions were considered to be serious. The risk to participants in this trial may be minimised by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring.

Where possible, endpoint data will be recorded and captured utilising the participant's electronic medical record, and study interventions will be kept to a minimum, in keeping with the implementation research methodology.

Women of child-bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the participant will not reliably comply, they should not be entered or continue in the study.

Overall, the risk-benefit of inclisiran is favorable for this clinical trial.

An expanded risk-benefit summary is provided in the Investigational Brochure.

4.6.1 Blood sample volume

A capillary blood sample will be taken for immediate analysis of the participants' lipid profile [redacted] at the initial screening/baseline visit, day 90 and again at the end of study (EOS) visit. A point of care testing machine will be used.

Additional blood samples may be required for safety monitoring.

Timings of blood sample collection are outlined in the assessment schedule (Section 8, Table 8-1).

5 Study Population

A total of 900 participants (300 per treatment group) at up to 30 primary care centres in the localised geographical region of Greater Manchester will be required for this study. The total duration of participant participation will be approximately 9 months (270 days).

This study will include male or female participants ≥18 years of age, who are on established lipid lowering medication, or have been recommended lipid lowering therapy by their health care provider but are unable to tolerate treatment.

Generalisability of the study population to the UK is essential; therefore, the study will be performed in a primary care setting across Greater Manchester and patients will be recruited by their GP. The Quality and Outcomes in Primary Healthcare clinical indicators (QOPH) demonstrate that chronic disease prevalence in Greater Manchester is comparable to the UK population as a whole (QOPH, 2018). Key data supporting the generalisability to the UK population is presented in Appendix 5.

5.1 Inclusion criteria

Participants eligible for inclusion in this study must meet **all** of the following criteria:

1. Signed informed consent must be obtained prior to participation in the study.
2. Male or female participants ≥18 years of age.
3. Patients on established lipid lowering medication, or have been recommended lipid lowering therapy by their health care provider but are unable to tolerate treatment.
4. A total cholesterol measurement at screening that is ≥4 mmol/L [approximately 160 mg/dL].
5. Participants on lipid-lowering therapies should be on a stable dose for ≥30 days before screening with no planned medication or dose change.

5.2 Exclusion criteria

Participants meeting any of the following criteria are not eligible for inclusion in this study.

1. Medical or surgical history that might limit the individual's ability to take study treatments for the duration of the study and/or put the participant at significant risk (e.g. severe respiratory disease; cancer or evidence of spread within approximately the last 5 years, other than non-melanoma skin cancer; or history of alcohol or substance misuse).
2. Current or planned renal dialysis or transplantation.
3. Acute coronary syndrome or stroke less than 4 weeks before the screening visit.
4. Coronary revascularization procedure planned within the next 6 months.
5. Women of child-bearing potential, unless they agree to abstinence or, if sexually active, agree to the use of effective methods of contraception during the study. The effective contraception methods are one of the following:
    - Barrier method of contraception (male or female condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository
    - Other more effective forms such as oral (estrogen and progesterone), injected or implanted combined hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception or total abstinence or male/female sterilisation
6. Women who are pregnant or breast-feeding.
7. Previous, current, or planned treatment with a monoclonal antibody targeting PCSK9, or with a drug known to be contra-indicated with inclisiran.
8. Previous exposure to inclisiran or participation in a randomised study of inclisiran.
9. Current or previous participation in a clinical study with an unlicensed drug or device within 30 days or five half-lives of the screening visit, whichever is longer.
10. Participants who plan to move away from the geographical area where the study is being conducted during the study period.
11. A triglyceride measurement at screening that is ≥4.52 mmol/L

6 Treatment

6.1 Study treatment

The study treatment, Inclisiran for Injection (SC use), is a sterile formulation of inclisiran sodium in water for injection packaged in vial or glass pre-filled syringe (PFS) presentations. The covid-19 vaccination should not be given within 7 days of receiving IMP.

6.1.1 Investigational drug

Table 6-1 Investigational drug

Product Name:	Inclisiran
Active ingredient	Inclisiran sodium
Dosage Form:	Solution for Injection
Unit Dose	Inclisiran sodium 300 mg/1.5 mL vial (equivalent to 284 mg inclisiran)
Route of Administration	Subcutaneous (SC) use
Physical Description	Clear, colorless to pale yellow solution essentially free of particulates
Manufacturer	Alcami Corporation, Charleston, South Carolina, United States of America.

6.1.2 Additional study treatments

Participants should be receiving a lipid-lowering therapy (such as a statin and/or ezetimibe) as background therapy, and should be on a stable dose for ≥30 days before screening with no planned medication or dose change prior to randomisation. This treatment will be provided as part of normal clinical practice.

Patients who have been recommended lipid lowering therapy by their HCP but are not able to tolerate their treatment are also eligible for this study. These patients may receive treatment with inclisiran alone and the proportion of these patients included in the study will be reported in patient demographics.

6.1.3 Treatment groups

Participants will be assigned at the baseline/screening visit to one of the following three treatment groups in a ratio of 1:1:1.

- **Group 1:** Participants will continue to receive their lipid-lowering background therapy plus behavioural support (see Appendix 1)
- **Group 2:** Participants will continue to receive their lipid-lowering background therapy plus inclisiran for injection (delivered in an injection-only model)
- **Group 3:** Participants will continue to receive their lipid-lowering background therapy, plus inclisiran for injection (delivered in an injection only model), plus behavioural support (see Appendix 1)

6.1.4 Post-Trial Access

It is anticipated that inclisiran will have received regulatory authority approval and will be available for HCPs to prescribe at the point at which this study ends. The investigator at each site should therefore determine whether the patient has derived clinical benefit and should be prescribed inclisiran as part of normal clinical practice following the end of the study. If regulatory authority approval has not been gained patients will revert back to standard of care following medication review by their GP.

6.1.5 Concomitant therapy

As this is a pragmatic trial, all medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the participant was enrolled into the study will be collected from the EMR to inform the outcomes of the study. Only relevant concomitant medications related to an AE will be manually entered in the eCRF.

Table 6-2 Therapy derived data

Concomitant therapy	Data to be entered into eCRF	Automated data collection (primary and secondary via available national datasets)
Demography	X	
Relevant medical history/current medical history		X
Composite cardiovascular risk	X	
HbA1c		X
Lipid profile [redacted]	X	
Adverse Events	X	
AE relevant concomitant medications and relevant medical history	X	
Concomitant medications		X
[redacted]		

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact the Novartis medical monitor before randomising a participant or allowing a new medication to be started. If the participant is already enrolled, contact Novartis/Sponsor to determine if the participant should continue participation in the study.

The following medications/treatments are **not permitted** to be added to existing therapy during the study:

- Medications prescribed to lower LDL-C (e.g. statins, ezetimibe, lomitapide, mipomersen, niacin, colesevelam, bile acid absorption inhibitors, monoclonal antibodies directed towards PCSK9).
- Any medication taken for the purpose of lipid lowering, including over-the-counter or herbal therapies.

6.2 Participant numbering, treatment assignment, randomisation

6.2.1 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned when the participant is enrolled for screening and is retained for the participant throughout his/her entire participation in the trial. The Participant No. consists of the Center Number (Centre No.), assigned by Novartis to the investigative site, with a sequential participant number suffixed to it, so that each participant is numbered uniquely across the entire database. Upon the participant signing the informed consent form, the participant is assigned to the next sequential Participant No. available. A new Participant No. will be assigned at every subsequent enrollment if the participant is re-screened.

6.2.2 Treatment assignment, randomisation

At the baseline visit, all eligible participants will be randomised via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the participant fulfils all the inclusion/exclusion criteria. The IRT will assign a randomisation number to the participant, which will be used to link the participant to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the participant.

The randomisation numbers will be generated using the following procedure to ensure that treatment assignment is unbiased. A participant randomisation list will be produced by the IRT provider using a validated system that automates the random assignment of participant numbers to randomisation numbers. These randomisation numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Global Clinical Supply (GCS) using a validated system that automates the random assignment of medication numbers to packs containing the study treatment. The randomisation scheme for participants will be reviewed and approved by a member of the Randomisation Office.

6.2.3 Recruitment cap

During recruitment the study team may consider it appropriate to cap the recruitment of patients who have an LDL-C <2.6mmol/L, in order to ensure the results remain generalisable for the purposes of NHS-E.

6.3 Dose escalation and dose modification

Investigational or other study treatment dose adjustments and/or interruptions are not permitted.

6.4 Additional treatment guidance

6.4.1 Treatment compliance

Participants assigned to Group 1 and Group 3 (See Section 6.1.3) will receive monthly telephone based behavioural support (see Appendix 1). As part of this programme, compliance will be promoted in regard to their regular prescribed medication, including lipid lowering

therapy. Participants in Group 2 and Group 3 (See Section 6.1.3) will be reminded to attend or be available for each administration of the study drug by the investigator or designated person. Participants will be encouraged to contact their GP practice if they miss their appointment. In addition to this participants may receive SMS text reminders for their appointments from their GP practice, as is common with clinical practice.

Adherence with study medication will be based on analysis of medications dispensed (for standard of care treatment) and administered (for inclisiran treatment) during the study.

6.4.2 Recommended treatment of adverse events

At present there is insufficient information to provide specific recommendations regarding treatment of adverse events (AEs).

Medication used to treat adverse events (AEs) must be recorded as appropriate within the eCRF (See Section 10).

6.5 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under investigational and control drugs section.

A unique medication number is printed on the study medication label.

As per the treatment assigned to the participant, investigator staff will select the study treatment to dispense to the participant. The study medication has a 2-part label (base plus tear-off label. Immediately before dispensing the package to the participant, site personnel will detach the outer part of the label from the package and affix it to the participant's source document.

6.5.1 Handling of study treatment and additional treatment

6.5.1.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels.

Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the participant except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug

accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.5.2 Instruction for prescribing and taking study treatment

Study drug injections will be performed by qualified clinical staff delegated by the investigator.

The site of injection is the abdomen; alternative injection sites include the upper arm or thigh. Injections should not be given into areas of active skin disease or injury such as sunburns, skin rashes, inflammation, tattoos or skin infections.

Participants will be administered one s.c. injection of study drug at pre-defined visits as specified in the Assessment Schedule (Section 8) and summarised below.

Participants randomised to group 2 or 3 will receive one injection of inclisiran on Day 1 and a second injection of inclisiran on Day 90.

Injections will be administered after all other study assessments have been completed for the visit.

Should a participant develop signs or symptoms of anaphylaxis when study drug is injected, the investigator or delegate will need to collect a blood sample for tryptase within 30 minutes of the onset of anaphylaxis (or as soon as possible).

All kits of study treatment assigned by the IRT will be recorded in the IRT system.

7 Informed consent procedures

Eligible participants may only be included in the study after providing (witnessed, where required by law or regulation) IRB/IEC-approved informed consent.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the participant source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). This information will be included in the participant informed consent and should be discussed with the participant during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the participant.

7.1 Participants who will be asked for consent

The following patient informed consents are included in this study:

- Main study consent, which also includes:

- Consent for patients to be contacted to participate in the Process Evaluation component of this study (as described in Section 4.3)
- As applicable, Pregnancy Outcomes Reporting Consent for female participants

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements.

Male participants must be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information.

The following Healthcare Professional and Commissioner consents are included in this study:

- Up to 50 HCPs and a minimum of 10 Commissioners will be approached for to participate in the Process Evaluation component of this study (as described in Section 4.3)
- HCPs and Commissioners will be asked to give consent for their participation in this element of the study prior to the Process Evaluation interviews (Section 7.2).

A copy of the approved version of all consent forms must be provided to Novartis after IRB/IEC approval.

7.2 Remote consent

In the event of a global health disruption event, such as a pandemic/epidemic (e.g. COVID-19), that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, the Investigator may conduct the informed consent discussion remotely (e.g. telephone, video conference).

7.3 Informed consent procedures for the process evaluation

All potential research respondents (patients, HCPs or Commissioners) who are recruited for telephone interviews as part of the process evaluation will receive verbal and written information (participant information sheet) regarding the study and will be encouraged to ask questions prior to taking part. It will be made clear that participation in the interview is purely voluntary and respondents are able to withdraw from the interview at any time, without giving a reason. Following the consent outlined above verbal consent will be confirmed before undertaking the telephone interview which we will audio-record separately to the interview audio-recording.

7.3.1 Confidentiality and anonymity

Once a participant (patient, HCP or Commissioner) gives consent to participate in the process evaluation, they will be provided with a unique identifier. This unique identifier is assigned for the purposes of the process evaluation. Audio recordings and transcriptions will be identified only by their unique identifier and not the name of the respondent. The key to the unique identifier and respondent's details will only be accessible to members of the study team and stored electronically on the University of Manchester secure server, separate to the de-identified data.

Transcription of audio-recordings will be undertaken by a University of Manchester approved external transcription company. Audio recordings will be uploaded to the transcription company via a secure server. We will remove any personal identifying information (such as names, places) from transcriptions once they are returned.

8 Visit schedule and assessments

The Assessment Schedule (Table 8-1) lists all of the assessments and when they will be performed.

Participants should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Participants who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled.

8.1 Domiciliary visits

In the event of a global health disruption event, such as a pandemic/epidemic (e.g. COVID-19), that limits or prevents the conduct of site study visits per protocol, special effort should be made to conduct on-site visits. If it is not feasible to conduct on-site visits, visits to the patient's home can be attempted. These visits will be performed by experienced HCPs with anaphylaxis training and following local guidelines and SOPs.

Table 8-1 Assessment schedule

Period	**Screening**	**Treatment**		
Visit Name	**Screening/ Baseline**	**Treatment Period**		**End of Study**
Day	(-14 to -1)	Day 1 (± 14 days)	Day 90 (± 14 days)	Day 270 (± 14 days)
Obtain informed consent	X			
Demography	X			
Inclusion/exclusion criteria	X			
Relevant / current medical history[1]	→	→	→	→
Height	X			X
[redacted]				
Smoking Status	X			X
Dietary advice status	X			X
Exercise status	X			X
[redacted]				
HbA1c[2]	X			X
Lipid profile[redacted]	X		X	X
Urine pregnancy test for WOCBP	X			
Adverse Events[4]	X	→	→	→
Prior/Concomitant Medications[5]	→	→	→	→

Period	**Screening**	**Treatment**		
Visit Name	**Screening/ Baseline**	**Treatment Period**		**End of Study**
Day	(-14 to -1)	Day 1 (± 14 days)	Day 90 (± 14 days)	Day 270 (± 14 days)
Patient Reported Outcomes (PAM) [6]	X		X	
Patient Reported Outcomes (CSQ-8)[6]			X	
[redacted]				
Behavioural Support Programme[7]		Participants in the inclisiran + behavioural support and standard of care + behavioural support arms will have access to this service throughout the study		
Process Evaluation[8]		→	→	
[redacted]				
Study drug administration		X	X	
IWRS/IRT Registration/Randomisation	X	X[10]	X	X

X = assessment to be recorded in the clinical database or received electronically from a vendor

[1] ConneXon Data Platform to automate regular collection from EMR.

[2] ConneXon Data Platform to automate collection of closest recorded value prior to the screening/baseline visit and EOS visit.

[3] Capillary sample to be taken for immediate analysis using a CardioChek device for analysis of lipid profile ([redacted] LDL-C and non-HDL).

[4] After screening/baseline visit all SAE's will be monitored and collected using ConneXon Data Platform (see Section 10).

[5] Use of ConneXon Data Platform to automate regular collection from EMR.

[redacted]

[7] The behavioural support programme consists of a telephone based support service providing advice on diet, lifestyle, medication adherence, and CV risk management. Patients will have access to a scheduled programme of delivery

[8] Process Evaluation interviews will be carried out in line with the study visits at Day 1 and Day 90.

[redacted]

[10] Patients randomised to Group 1 do not need to attend this visit but can have a phone call instead

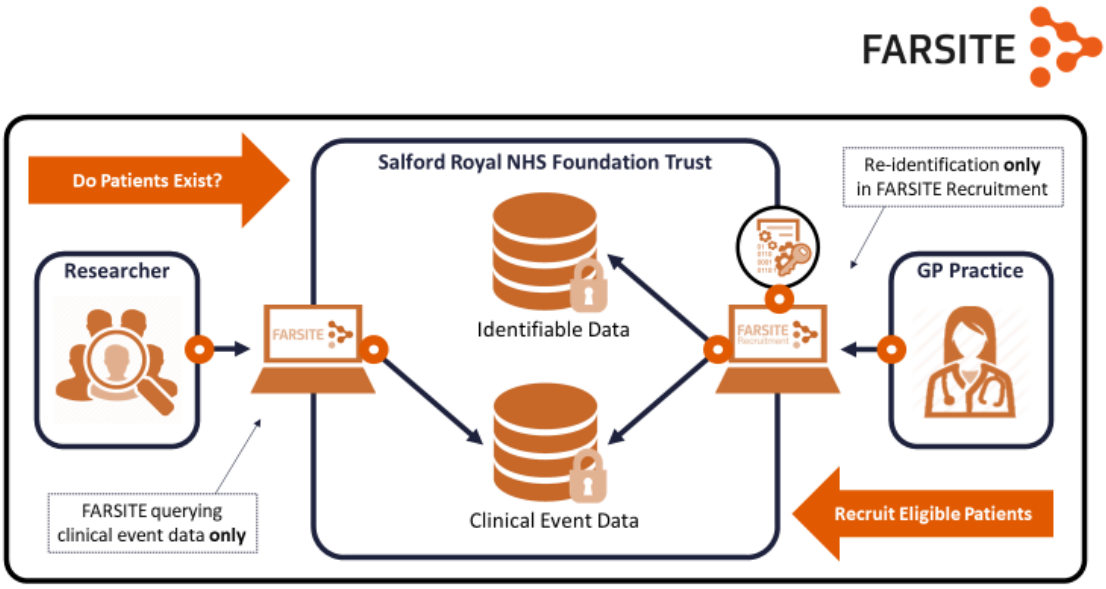
8.2 Screening

Screening (Days -14 to -1)

Eligibility and recruitment to the study will be optimised by using NWEH's proven feasibility and recruitment system FARSITE.

FARSITE, is a tool for searching, finding, and contacting patients with research opportunities, whilst still preserving their confidentiality. The principle behind FARSITE is to maintain patient confidentiality by anonymising the information given to researchers, and only allowing GPs to decide whether their patient should be contacted. Researchers do not have access to individual patient records, information about individuals who meet the criteria for a protocol is only available to the patient's GP practice. All identifiable records are seen only by the GP as the data controller, and a handful of NWEH and Salford Royal Foundation Trust (SRFT) technical staff by exception to maintain the FARSITE system. Researchers see only de-identified records, as the datasets are held in two different databases stored securely on the N3 NHS network (see Figure 8-1).

Figure 8-1 FARSITE System Overview



NWEH researchers will use the FARSITE Feasibility view which contains anonymised data during the initial stages of recruitment to see how many patients match the study protocol; the numbers of patients matching each inclusion criterion; and the numbers belonging to each registered GP practice. FARSITE will identify and be used to contact the most suitable GP practices within Greater Manchester to ascertain the maximum number of patients from up to 30 GP practices. Once the list of potential patients is identified, the GP will review the patient's medical records manually and confirm eligibility. There are no screening laboratory tests

required to be performed for this study, total cholesterol inclusion criteria will be determined by the pathology results available in the patients EMR.

The following procedures will be performed within 14 days prior to study treatment:

- Informed consent
- Assessment of inclusion and exclusion criteria
- Demographics
- Vital signs (height,)
- CV risk (smoking status, diet, exercise, HbA1c if available)
- Lipid profile
- Randomisation

It is permissible to re-screen a participant if s/he fails the initial screening; however, each case must be discussed and agreed with the Sponsor on a case-by-case basis and can be only once per patient during the study period.

8.2.1 Information to be collected on screening failures

Participants who sign an informed consent form and are subsequently found to be ineligible prior to randomisation will be considered a screen failure. The reason for screen failure should be recorded on the eCRF. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event during the screening phase (see SAE section for reporting details). If the participant fails to be randomised, the IRT must be notified within 2 days of the screen fail that the participant was not randomised.

Participants who are randomised and fail to start treatment, e.g. participants randomised in error, will be considered an early terminator. The reason for early termination should be recorded on the appropriate eCRF.

8.3 Participant demographics/other baseline characteristics

Baseline demographic information will be collected during screening/baseline visit and will include age, sex and race/ethnicity. These data will be recorded in the eCRF.

Relevant medical and surgical history recorded within the last 5 years will be extracted from the EMR from the date of consent. (see Section 6.1.5 Table 6-2)

Concomitant medication taken within the last 5 years will be extracted from the participants' primary care EMR from date of consent.

Cardiovascular risk assessment

Information required to assess composite cardiovascular risk will include;

- Height - measured at screening/baseline visit and EOS visit

- [redacted]
- Smoking status -collected at screening/baseline visit and EOS visit
- Dietary advice status -collected at screening/baseline visit and EOS visit
- Exercise status (calculated using Physical Activity Index (PAI) see Appendix 6) - collected at screening/baseline visit and EOS visit

These data will be recorded in the eCRF.

- HbA1c- if available the closest recoded value prior to the screening/baseline visit and EOS visit to be extracted from the EMR.

8.4 Efficacy Assessments

Lipid Profile[redacted]

A capillary blood sample will be taken for immediate analysis of the participant's lipid profile[redacted] for assessment of efficacy. This will be performed at screening/baseline visit, day 90 visit and EOS (day 270) visit (see Assessment Schedule Table 8-1).

Parameters to be assessed include:

- [redacted]
- Non-HDL (calculated)
- LDL-C calculated using Friedewald

These data will be recorded in the eCRF

Patient Reported Outcomes Questionnaires

The Client Satisfaction Questionnaire and Patient Activation Measure (PAM) questionnaire will be administered after treatment at day 90. Patients will take the questionnaires to complete after the study visit and return them via post.

The Process Evaluation

The process evaluation will be conducted by Manchester University using the Consolidated Framework for Implementation Research (CFIR).

8.4.1 Efficacy assessment - Primary

- Percentage change in LDL-C from baseline to day 270

8.4.2 Efficacy assessment - Secondary

- CSQ administered after treatment at day 90.
- PAM questionnaire administered after treatment at day 90.
- Process evaluation

8.5 Safety

8.5.1 Pregnancy

Females of child-bearing potential are defined as all females physiologically capable of becoming pregnant.

Serum/urine pregnancy tests will be performed for all females of child-bearing potential according to the Assessment Schedule (Table 8-1). A positive urine pregnancy test should be confirmed with a serum pregnancy test. Additional pregnancy tests may be performed at the investigator's discretion during the study and/or if requested by local requirements.

Participants becoming pregnant must be discontinued from study drug. However, a participant may choose to remain in the study should she become pregnant, and be followed according to the protocol-defined study visits.

8.5.2 SAEs

All SAEs whatever the causal relationship to the research, AEs leading to study treatment discontinuation and other situations relevant to the safety (pregnancy and treatment errors) (see Section 10.3.4. and 10.3.5) of the participants must be followed up and fully and precisely documented in order to ensure that the sponsor has the necessary information to continuously assess the benefit-risk balance of the clinical trial.

8.6 Laboratory assessments

There are no regular laboratory tests required by this protocol. All blood tests will be performed locally by clinical pathology laboratories, in common with usual practice. Methods for sampling, handling and analysis will be the same as usually applied in routine care.

Abnormal laboratory findings, that are detected during the study or are present at baseline and significantly worsen following study drug administration, and are deemed as clinically significant by the investigator will be recorded as AEs if they lead to treatment discontinuation (or SAEs if they meet the definition see Section 10).

9 Study discontinuation and completion

9.1 Discontinuation and completion

9.1.1 Study treatment discontinuation and study discontinuation

Discontinuation of study treatment for a participant occurs when study treatment is stopped earlier than the protocol planned duration and can be initiated by either the participant or the investigator.

The investigator must discontinue study treatment for a given participant if he/she believes that continuation would negatively impact the participant's well-being.

Study treatment must be discontinued under the following circumstances:

- Participant decision

- Pregnancy
- Use of prohibited treatment as per recommendations in the prohibited treatment section
- Any situation in which study participation might result in a safety risk to the participant

Emergence of the following adverse events:

- Any laboratory abnormalities that in the judgment of the investigator, *taking into consideration the participant's overall status,* prevents the participant from continuing participation in the study
- Severe hypersensitivity reaction occurs, including the following: anaphylaxis associated with, fever, chills, urticaria, dyspnea, headache, myalgia, hypotension.

If discontinuation of study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the participant's premature discontinuation of study treatment and record this information.

Participants who discontinue study treatment should NOT be considered withdrawn from the study UNLESS they explicitly withdraw their consent (see Section 9.1.2 Withdrawal of Informed Consent' section). **Where possible, they should be encouraged to return for the assessments indicated** in the Assessment Schedule. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the participant/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

Participants who discontinue treatment without withdrawing consent are effectively allowing use of their data via the electronic system for the purposes of evaluating many of the study endpoints, e.g. for the equivalent of the protocol-defined 9 month study interval.

The investigator must also contact the IRT to register the participant's discontinuation from study treatment.

Participants who discontinue study treatment or withdraw consent from the study will not be replaced.

9.1.2 Withdrawal of informed consent

Participants may voluntarily withdraw consent to participate in the study for any reason at any time.

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the participant's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the participant are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study discontinuation. A final evaluation at the time of the participant's study discontinuation should be made as detailed in the assessment table.

Novartis will continue to retain and use all research results (data) that have already been collected for the study evaluation.

9.1.3 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the participant, e.g. dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination:

- Unexpected, significant, or unacceptable safety risk to participants enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of study drug development

In taking the decision to terminate, Novartis will always consider participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible and treated as a prematurely withdrawn participant. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests. The investigator or sponsor depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last participant finishes their EOS visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator or, in the event of an early study termination decision, the date of that decision.

All randomised and/or treated participants will be remotely monitored for safety events using ConneXon trials platform 30 days after their EOS visit. All SAEs reported during this time period must be reported as described in Section 10.

Continuing care should be provided by the investigator and/or referring physician based on participant availability for follow-up.

This care may include:

- Enrollment in a follow-up study, if participants are eligible

10 Safety monitoring and reporting

10.1 Definition of adverse events

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a clinical investigation participant after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

10.1.2 Serious adverse events

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s), or medical conditions(s) which meets any one of the following criteria:

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the participant was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalisation or prolongation of existing hospitalisation, unless hospitalisation is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent form
  - social reasons and respite care in the absence of any deterioration in the participant's general condition
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardises the participant or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the participant or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalisation or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

All new malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met and the malignant neoplasm is not a disease progression of the study indication.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

10.2 Reporting requirements for adverse events

In this study, only SAEs will be detected, documented and reported. AEs leading to treatment discontinuation will be documented.

- The investigator or delegate has the responsibility for managing the safety of individual participants and identifying and reporting events that meet the definition of AE leading to treatment discontinaution, and SAEs.
- Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.
- NWEH's ConneXon trials platform will be utilised for remote safety monitoring. Using this technology all [redacted] SAEs will be alerted to the study team. SAEs will be reported to the sponsor within 24 hours of awareness.
- AEs also may be detected when they are volunteered by participants during or between visits or other assessments such as when the patient reported outcomes questionnaires (CSQ-8, PAM [redacted]) are returned to the study team (see 16.2 Appendix 2: The CSQ-8 PROMs Questionnaire, 16.3 Appendix 3: The PAM PROMs Questionnaire and 16.4 Appendix 4: [redacted]).

10.3 Collection and assessment of adverse events

10.3.1 Adverse event severity

The severity of AE will be assessed by the investigator or delegate.

- **mild:** usually transient in nature and generally not interfering with normal activities
- **moderate**: sufficiently discomforting to interfere with normal activities
- **severe:** prevents normal activities

10.3.2 Relationship to study treatment

The relationship between the AE and the investigational product will be assessed using a binary assessment. The investigator should determine whether there is a reasonable suspected causal relationship to the medicinal product based on the definitions below:

- **Suspected relationship** - There is a reasonable possibility that the administration of the investigational product caused the AE. There is evidence to suggest a causal relationship between the investigational product and the AE

- **Not suspected relationship-** There is no reasonable possibility that the administration of the investigational product caused the AE. There is no temporal relationship between the investigational product and event onset, or an alternative etiology has been established

If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single participant

- Its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported
- Whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
- Action taken regarding study treatment.

The Investigator will have the ultimate responsibility for determining causality and seriousness. In the interim period, until the Investigator review, the opinion of the appropriately delegated research nurse will be used for collecting and reporting. If the research nurse suspects a causal relationship to an AE, this will be escalated to the Investigator for immediate review.

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- Dose not changed
- Drug interrupted/withdrawn
- Its outcome (i.e. recovery status or whether it was fatal)

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent (e.g. continuing at the end of the study), and assessment must be made at regular intervals of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure (IB).

Adverse event monitoring should be continued for at least 30 days following the EOS visit.

10.3.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 30 days after the EOS visit must be reported to Novartis safety within 24 hours of learning of its occurrence.

Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator or delegate receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, Chief Medical Office and Patient Safety (CMO & PS) Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the 30 day period should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

10.3.4 Pregnancy reporting

Pregnancies

If a female trial participant becomes pregnant, the study treatment should be stopped, and the trial participant must be asked to read and sign a pregnancy consent form to allow the investigator to ask about her pregnancy. To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up until one year after birth to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the investigator to the CMO&PS. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the *study treatment* and pregnancy outcome. Any SAE experienced during pregnancy must be reported.

10.3.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a HCP, participant or consumer (European Medicines Agency (EMA) definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate eCRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dosing eCRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE leading to treatment discontinuation	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see the respective sections.

11 Data Collection and Database management

11.1 Data collection

Data not requiring a separate written record will be defined in the protocol and the Assessment Schedule (Section 8, Table 8-1) and can be recorded directly on the eCRFs. All other data captured for this study will have an external originating source (either written or electronic) with the eCRF not being considered as source.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

Designated investigator staff will enter the data required by the protocol into the participant casebooks within the Electronic Case Report Form (eCRF). The eCRF has been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, research staff will not be given access to the eCRF until they have been trained. Automatic validation programs check for data discrepancies in the eCRF, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (entered into the eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

After final database lock of the eCRF, the investigator will receive copies of the participant data for archiving at the investigational site.

This study will also use electronic technology to collect source data automatically, using an electronic system (the "Data Platform") to capture source data files. Information to be originally captured and controlled via automated means includes medical histories, concomitant medications, and primary and secondary healthcare interactions throughout the course of the

study. Data collected automatically in this way will be used for both remote monitoring of subject safety, and for study data analyses. Research staff have no access to the Data Platform system.

Both the eCRF and the Data Platform systems meet the fundamental elements of data quality (e.g. attributable, legible, contemporaneous, original, and accurate) that are expected of paper records in FDA guidance, are fully validated and conform to 21 CFR Part 11 requirements.

11.2 Database management and quality control

Data will be entered into a fully validated study database by the NWEH study team. Central Data Management will be completed in line with NWEH Central Data Management and Monitoring procedures.

Data Quality will be accomplished by a combination of automated data validation queries and manual Central Data Management completed by the NWEH Clinical Data Management (CDM).

All eCRF forms will require monitoring by the CDM and marking as Data Quality Review Complete.

Queries are raised within the eCRF and their response and resolution will be managed by the CDM within defined timelines. Designated research staff are required to respond promptly to queries and to make any necessary changes to the data.

PROM questionnaires will be completed by participants in a paper format, and reviewed for completeness by the study team and then transcribed in to the eCRF.

Events, interventions and findings derived from the electronic data will be collected and converted into Structured Data Tabular Model (SDTM) by NWEH before sending to Novartis for analysis. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology by Novartis and NWEH.

Dates of screenings, randomisations, screen failures and study completion, as well as randomisation codes and data about all study treatment (s) dispensed to the participant will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis and NWEH at specific timelines.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis/ representative will review the protocol and data capture requirements (i.e. eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of participant records, the accuracy of data capture /

data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralised Novartis CRA organisation. Additionally, a central analytics organisation may analyse data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The investigator or delegate must maintain source documentation for each participant in the study, consisting of hospital or clinic electronic medical records containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on eCRFs must be traceable to source documents in the EMR and participant's site file. The investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the participants will be disclosed.

11.3.1 Remote study initiation and monitoring visits

In the event of a global health disruption event, such as a pandemic/epidemic (e.g. COVID-19), requiring social distancing or limited travel/attendance to site, remote site initiation and monitoring could be considered.

12 Data analysis and statistical methods

Details of the statistical analysis and data reporting will be summarised in the Statistical Analysis Plan (SAP) document finalised before data lock. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation. Efficacy and safety analyses will be performed after all participants have completed the Day 270 visit or discontinued prior to the Day 270 visit. All available data from the clinical database will be included in the analysis.

12.1 Analysis sets

The Full Analysis Set (FAS) comprises of all randomised participants with the exception of those mis-randomised participants who did not receive study drug. Mis-randomised participants are defined as not qualified for randomisation and are inadvertently randomised into the study. According to the intent to treat principle, participants will be analysed according to the treatment they have been assigned to during the randomisation procedure. The FAS will be used in analyses for the primary, secondary, [redacted] efficacy objectives.

The Safety Set includes all participants who received at least one dose of study treatment. Participants will be analysed according to the study treatment received. This will be the primary population for the safety analyses.

12.2 Participant demographics and other baseline characteristics

Demographic and other baseline data including medical history will be summarised descriptively by treatment group for the FAS.

Categorical data will be presented as frequencies and percentages by treatment group. For continuous data, non-missing observations, mean, standard deviation, median, minimum, and maximum will be presented. For continuous data, the 1st and 3rd quartile will also be presented by treatment group.

Relevant medical histories and current medical conditions at baseline will be summarised separately by system organ class and preferred term, by treatment group. Histories of statin intolerance will be summarised by treatment group.

12.3 Treatments

The Safety set will be used for the analyses below.

The number of participants dosed at each dosing visit, number of study doses administered, duration of exposure in days, and dose administered will be summarised by treatment group.

Lipid-modifying therapy use at screening and the baseline/Randomisation visit (Day 1) will be summarised by treatment group. New or changed lipid-modifying therapy after baseline will be summarised by treatment group.

Other concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be summarised according to the Anatomical Therapeutic Chemical (ATC) classification system, by treatment group.

12.4 Analysis of the primary endpoint(s)/estimand(s)

12.4.1 Definition of primary endpoint(s)/estimand(s)

The primary effectiveness question of interest is: What is the effect of the test treatment inclisiran (+/- behavioural support) and standard of care + behavioural support on change in LDL-C after 270 days of treatment in adults on established lipid lowering medication or who have been recommended lipid lowering therapy by their health care provider but are unable to tolerate treatment, regardless of treatment discontinuation for any reason and regardless of unforeseen change in the concomitant lipid lowering therapy.

The justification for the primary estimand is that it will capture both the effect of the study drug and the effect of changes in additional medication(s) used for lipid lowering, if they occur, in a primary care setting.

The primary estimand is described by the following attributes:

1. Population: Adults with elevated LDL-C on established lipid lowering medication or, have been recommended lipid lowering therapy by their health care provider but are unable to tolerate treatment. Further details about the population are provided in Section 5.

2. Endpoint: Percentage change in LDL-C from baseline to Day 270.

3. Treatment of interest: The randomised treatment (inclisiran alone or inclisiran with behavioural support) as add-on to the control treatment of lipid-lowering background therapy plus behavioural support. The type and dose of the concomitant lipid-lowering therapy should remain stable during the study. Further details about the investigational treatment and control treatment are provided in Section 6.

The summary measure: difference between treatments in least squares mean percentage change at Day 270.

The strategy for handling intercurrent events (treatment discontinuation, use of prohibited medications, deviation in background treatment or death) will be described in the SAP.

12.4.2 Statistical model, hypothesis, and method of analysis

The primary effectiveness objective of this study is to demonstrate superiority of each inclisiran (+/- behavioural support) arm compared to standard of care + behavioural support in terms of the percentage change from baseline in LDL-C to Day 270 in adults with elevated LDL-C. The statistical hypotheses that will be tested for each inclisiran arm are as follows:

- H0: The difference between participants treated with inclisiran (+/- behavioural support) and standard of care + behavioural support in the least squares mean percentage change from baseline to the Day 270 visit in LDL-C= 0
- Ha: The difference between participants treated with inclisiran (+/- behavioural support) and standard of care + behavioural support in the least squares mean percentage change from baseline to the Day 270 visit in LDL-C < 0

The primary analysis will use an analysis of covariance model (ANCOVA) on the percent change in LDL-C from baseline to Day 270 to test the superiority of inclisiran (+/- behavioural support) over standard of care + behavioural support after missing data imputation. The model will include a fixed effect for treatment and the baseline LDL-C value. Multiple imputation will be used to impute missing data using a washout model. A total of 100 imputed datasets will be created. The model will be fitted to each imputed dataset, and results will be combined using Rubin's combination rules. The difference in least squares means between treatment groups and corresponding 2-sided 95% confidence intervals will be calculated. The FAS will be used for this analysis. Full details on the model and imputation will be provided in the SAP.

The washout model will be used to explore the assumption that missing Day 270 visit data are missing not at random in participants in the inclisiran groups who discontinue the study treatment early before the Day 270 visit and cannot be followed for scheduled LDL-C assessments. Early terminating participants in the standard of care + behavioural support group will have missing data imputed based on the missing at random assumption. Full details will be provided in the SAP.

The family-wise error rate for comparisons of the two inclisiran arms with the lipid-lowering background therapy plus behavioural support arm will be controlled using the Holm procedure.

12.4.3 Handling of remaining intercurrent events of primary estimand

No remaining intercurrent events beyond those described above (treatment discontinuation, use of prohibited medications, deviation in background treatment or death) are expected.

12.4.4 Handling of missing values not related to intercurrent event

Other missing data are expected to be intermittent missing data and will be assumed to be missing at random. Imputation details for data missing at random in the washout model will be provided in the SAP.

12.4.5 Sensitivity analyses for primary endpoint/estimand

Sensitivity analyses to assess the robustness of the estimation in the presence of deviations from the assumptions specified in the primary analysis will be specified in the SAP.

12.4.6 Supplementary analysis

Details of supplementary analyses will be specified in the SAP (if required).

12.4.7 Supportive analyses

No supportive analyses are planned.

12.5 Analysis of secondary endpoints/estimands

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

The following are key secondary efficacy endpoints:

- Mean difference in total score using the validated CSQ-8 (Client Satisfaction Questionnaire) administered after treatment at day 90.
- Mean difference in total score using the validated Patient Activation Measure (PAM) questionnaire administered after treatment at day 90.
- Measures of adherence to cardiovascular disease self-management using the validated Patient Activation Measure (PAM) questionnaire administered after treatment at day 90 and using assessment of medication adherence during the study period.
- A process evaluation conducted using the Consolidated Framework for Implementation Research (CFIR)

The analysis methodology used for the process evaluation is described separately in Section 4.3.

The key secondary endpoints will be analysed using an ANCOVA model that includes treatment and baseline value (as appropriate). Full details, including possible sensitivity analyses, will be provided in the SAP.

Descriptive summaries by treatment group will be presented.

12.5.2 Safety endpoints

For all safety analyses, the safety set will be used. All tables will be presented by treatment group.

Safety summaries (tables, figures) include only treatment emergent events (events started after the first dose of study medication or events present prior to start of double-blind treatment but increased in severity based on preferred term) with the exception of baseline data which will also be summarised where appropriate (e.g. change from baseline summaries). In addition, a separate summary for deaths including on treatment and post treatment deaths will be provided.

In particular, summary tables for adverse events (AEs) will summarise only treatment emergent AEs.

Adverse events

The number (and percentage) of participants with serious adverse events and treatment emergent adverse events leading to discontinuation (started after the first dose of study medication) will be summarised in the following ways:

- by treatment, primary system organ class and preferred term.
- by treatment, primary system organ class, preferred term and maximum severity.
- by treatment, Standardised MedDRA Query (SMQ) and preferred term.

Separate summaries will be provided for study medication related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation.

A participant with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

Adverse events which will be counted for a specific treatment period are those which are treatment-emergent. These events are those with an onset after the start of the treatment period, or which were present prior to the start of the treatment period but increased in severity, changed from being not suspected to being suspected of study drug relationship, or developed into SAEs after the start of the treatment period.

[redacted]

12.6 [redacted]

[redacted]

[redacted]

12.7 Interim analyses

There are no interim analyses planned for this study.

12.8 Sample size calculation

The primary effectiveness endpoint of the study is percent change of LDL-C from baseline. However, the sample size is driven by patient experience (CSQ-8) and patient activation (PAM); two key secondary outcomes in this trial. Although these outcomes are increasingly used in pragmatic and implementation trials, there is less consensus over 'clinically meaningful' differences for such outcomes. The trial has been powered to detect differences equivalent to a Cohen's effect size of 0.3, approximating a 'small-to-medium' effect in conventional terms (Cohen 1988). This would be consistent with effect sizes in pragmatic, primary care trials using self-reported health outcomes, and with similar outcomes in a recent systematic review on coaching among patients with cardiovascular risk factors (An 2020). A sample size of 300 patients per arm would be able to detect this effect size with 90% power using a one-sided significance level of 0.025 (this includes a 20% allowance for drop-out in this primary care setting).

This sample size could also detect a reduction of at least 10% change of LDL-C from baseline in the inclisiran group (+/- behavioural support) compared to the standard of care + behavioural support group (assuming a standard deviation of 30% in the control group and 20% in the inclisiran group (+/- behavioural support) based on observed results from previous inclisiran studies).

The total sample size for the study will be 900 participants.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonised Tripartite Guidelines for Good Clinical Practice, with applicable local

regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, participant recruitment procedures (e.g., advertisements) and any other written information to be provided to participants. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (defined as last patient last visit) and finalisation of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of participants should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any

additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and Health Authorities, where required, it cannot be implemented.

14.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for participant safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

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16 Appendices

Appendix 1	Behavioural support programme
Appendix 2	The CSQ-8 PROMs Questionnaire
Appendix 3	The PAM PROMs Questionnaire
Appendix 4	[redacted]
Appendix 5	Generalisability of the Greater Manchester Population to the UK
Appendix 6	Calculating the 4-level Physical Activity Index (PAI)

16.1 Appendix 1: Behavioural Support Programme

To determine whether additional supported care can improve health behaviour, self-efficacy and health status, consented participants randomised to Group 1 and Group 3 will receive monthly telephone-based support call.

Behavioural Support will consist of a telephone-based lifestyle intervention to motivate and support participants to make effective choices for improving self-management including behaviour change, goal setting and empowerment.

This model of behavioral support is based on a well-established service involving non-clinical health advisors trained in motivational interviewing techniques. This was first developed from the Pro-active Call Centre Treatment Support randomised controlled trial (Young et al 2005) which demonstrated that pro-active healthcare adviser support improves glucose control in people with type 2 diabetes.

The telephone-based, lifestyle intervention will provide monthly support to enable participants to make positive behaviour changes. An initial call will be delivered by a health advisor and is focused on action planning to ensure each participant understands their diagnosis, the importance of reducing CV risk and taking medications correctly and how they can reduce their own risk. A lifestyle goal is then set together to help begin to achieve this, and participants will receive a pack of information, on CV disease and advice on healthy eating to help participants with goal setting and facilitate their understanding of risk.

The remainder of the programme is delivered by dedicated health advisors and consists of monthly telephone calls sequentially covering diet, exercise, medication and where necessary additional advice about glucose management and smoking cessation.

The behavioural support programme will be provided by a qualified medical support team.

16.2 Appendix 2: The CSQ-8 PROMs Questionnaire

The Client Satisfaction Questionnaire© (CSQ) is a portfolio of measurement instruments (CSQScales®) designed to assess consumer satisfaction with health and human services, including governmental and public benefit programs and services. It is derived from the work of Larsen et al. 1979.

The CSQ scales are well-validated and have been used extensively in the healthcare environment for comparison of interventions, clinical trials, clinical epidemiology, community epidemiology studies and field studies (https://csqscales.com/faqs/). Each scale measures the recipients' direct satisfaction with specific services offered and received within a particular time frame from a specific provider or service setting.

The CSQ-8 is the standard self-administered CSQ scale containing 8 items that comprise the measurement of satisfaction with services and measurement of improvement of capacity to cope and change adaptively. Items include questions enquiring about respondents' opinions and conclusions about services they have received or are currently receiving. Response options differ from item to item, but all are based on a four-point scale. Examples include: "How satisfied are you with the amount of help you have received?" (which response options: 1 = "Quite dissatisfied", 2 = "Indifferent or mildly dissatisfied", 3 = "Mostly satisfied", 4 = "Very satisfied"; and, "Have the services you received helped you to deal more effectively with your problems?" (Which has the response options: 4 = Yes, they helped a great deal", 3 = "Yes, they helped somewhat", 2 = "No, they didn't help", 1 = "No, they seemed to make things worse".

All items are positively worded; however, the directionality of response options span the spectrum from very negative to very positive; and the numerical anchors for items are reversed randomly (from high to low or low to high) from item to item to minimise stereotypic response sets. While addressing several elements that contribute to service satisfaction, the CSQ-8 has no subscales and reports a single score measuring a single dimension of overall satisfaction.

Scoring the CSQ-8

A total score is produced by summing all item responses, with a higher scores indicating higher satisfaction. The outcome is the mean difference in total score between treatment groups (Attkisson and Zwick, 1982). For the CSQ-8 version, scores range from 8 to 32, with higher values indicating higher satisfaction. Scoring for other versions is similar after extrapolating for number of items.

CSQ-8 UK English

CLIENT SATISFACTION QUESTIONNAIRE

CSQ-8

Please help us improve our service by answering some questions about the help that you have received. We are interested in your honest opinions, whether they are positive or negative. *Please answer all of the questions.* We also welcome your comments and suggestions. Thank you very much. We appreciate your help.

CIRCLE YOUR ANSWERS

1. How would you rate the quality of service you received?

4 *Excellent*	3 *Good*	2 *Fair*	1 *Poor*

2. Did you get the kind of service you wanted?

1 *No, definitely not*	2 *No, not really*	3 *Yes, generally*	4 *Yes, definitely*

3. To what extent has our service met your needs?

4 *Almost all of my needs have been met*	3 *Most of my needs have been met*	2 *Only a few of my needs have been met*	1 *None of my needs have been met*

4. If a friend were in need of similar help, would you recommend our service to him or her?

1 *No, definitely not*	2 *No, I don't think so*	3 *Yes, I think so*	4 *Yes, definitely*

5. How satisfied are you with the amount of help you received?

1 *Quite dissatisfied*	2 *Indifferent or mildly dissatisfied*	3 *Mostly satisfied*	4 *Very satisfied*

6. Have the services you received helped you to deal more effectively with your problems?

4 *Yes, they helped a great deal*	3 *Yes, they helped somewhat*	2 *No, they really didn't help*	1 *No, they seemed to make things worse*

7. In an overall, general sense, how satisfied are you with the service you received?

4 *Very satisfied*	3 *Mostly satisfied*	2 *Indifferent or mildly dissatisfied*	1 *Quite dissatisfied*

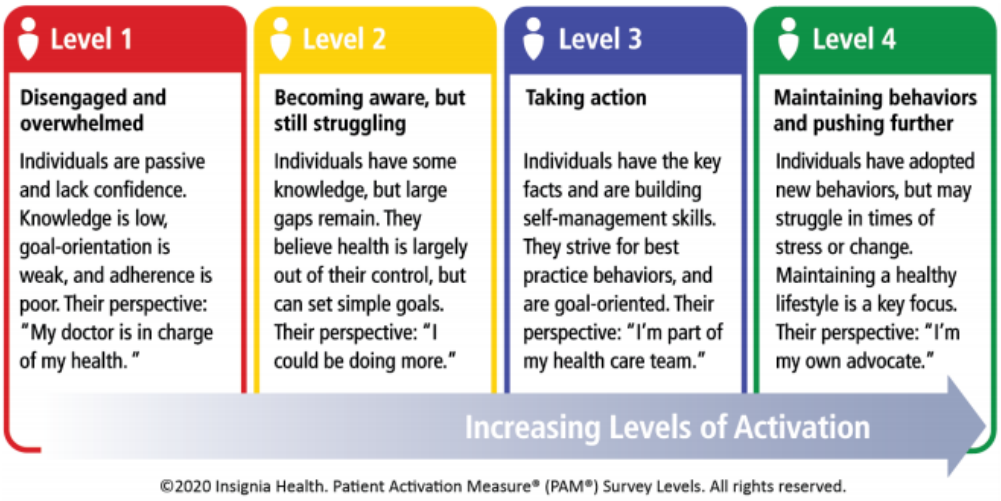
8. If you were to seek help again, would you come back to our service?

1 *No, definitely not*	2 *No, I don't think so*	3 *Yes, I think so*	4 *Yes, definitely*

16.3 Appendix 3: The PAM PROMs Questionnaire

The Patient Activation Measure (PAM®) questionnaire is a 10- or 13-item survey that assesses a person's underlying knowledge, skills and confidence integral to managing his or her own health and healthcare (https://www.insigniahealth.com/products/pam-survey). It is validated and has been supported by NHS-E to use across the NHS.

The PAM segments individuals into one of four activation levels along an empirically derived 100-point scale. Each level provides insight into an extensive array of health-related characteristics, including attitudes, motivators, and behaviors. Individuals in the lowest activation level do not yet understand the importance of their role in managing their own health, and have significant knowledge gaps and limited self-management skills. Individuals in the highest activation level are proactive with their health, have developed strong self-management skills, and are resilient in times of stress or change.



The PAM can be used to assess patient support strategies and programmes, and is reliable and validated for use with all patients, including those managing chronic conditions and engaged in disease prevention efforts. PAM is widely used today in population health management programs, disease and case management systems, wellness programs, medical home projects, care transitions, value-based programs, and much more.

This study will use the 13-point PAM questionnaire, which will be complemented by data on medication adherence to inclisiran or standard of care recorded during the trial. The 13 item PAM consists of 13 statements relating to patients beliefs about health care, confidence in their management of health related tasks, and self-assessed knowledge of their condition (Hibbard and Gilburt, 2014). For each statement patients are required to say how much they either agree or disagree on a response scale of 1–5, where 1 represents "strongly disagree", 4 represents "strongly agree" and 5 indicates that the statement is "not applicable" to them.

A standardised spreadsheet in excel is used to score the PAM. Responses are used to generate a continuous score from 0 to 100 where higher scores indicate that the patient is more activated (Hibbard and Gilburt, 2014). Where participants have answered that a statement is not

applicable to them the data is treated as missing. A total score is generated where participants have answered at least 10 out of the 13 questions.

The continuous PAM scores are then categorised into four levels for descriptive purposes using a calibration table. Those who fall into Level 1 are defined as passive recipients of care who do not understand that they can play an active role in their own healthcare. Level 2 includes patients who lack the basic knowledge and confidence to effectively self-manage (for example they may not understand the treatment options available to them or what their medications do). Level 3 includes those who have a basic knowledge about their health but they lack the confidence and skills to engage in positive self-management behaviours. Level 4 is for patients who have the knowledge and confidence to self-manage but who may need support during times of personal stress or health crisis (Hibbard et al, 2005).

The PAM has been found to be a valid and reliable measure in people with long-term conditions, such as those attending cardiac rehabilitation, (Hibbard et al, 2004) and in those patients with multi-morbidity (Skolasky et al, 2011).

Below are some statements that people sometimes make when they talk about their health. Please indicate how much you agree or disagree with each statement as it applies to you personally by circling your answer. Your answers should be what is true for you and not just what you think others want you to say.

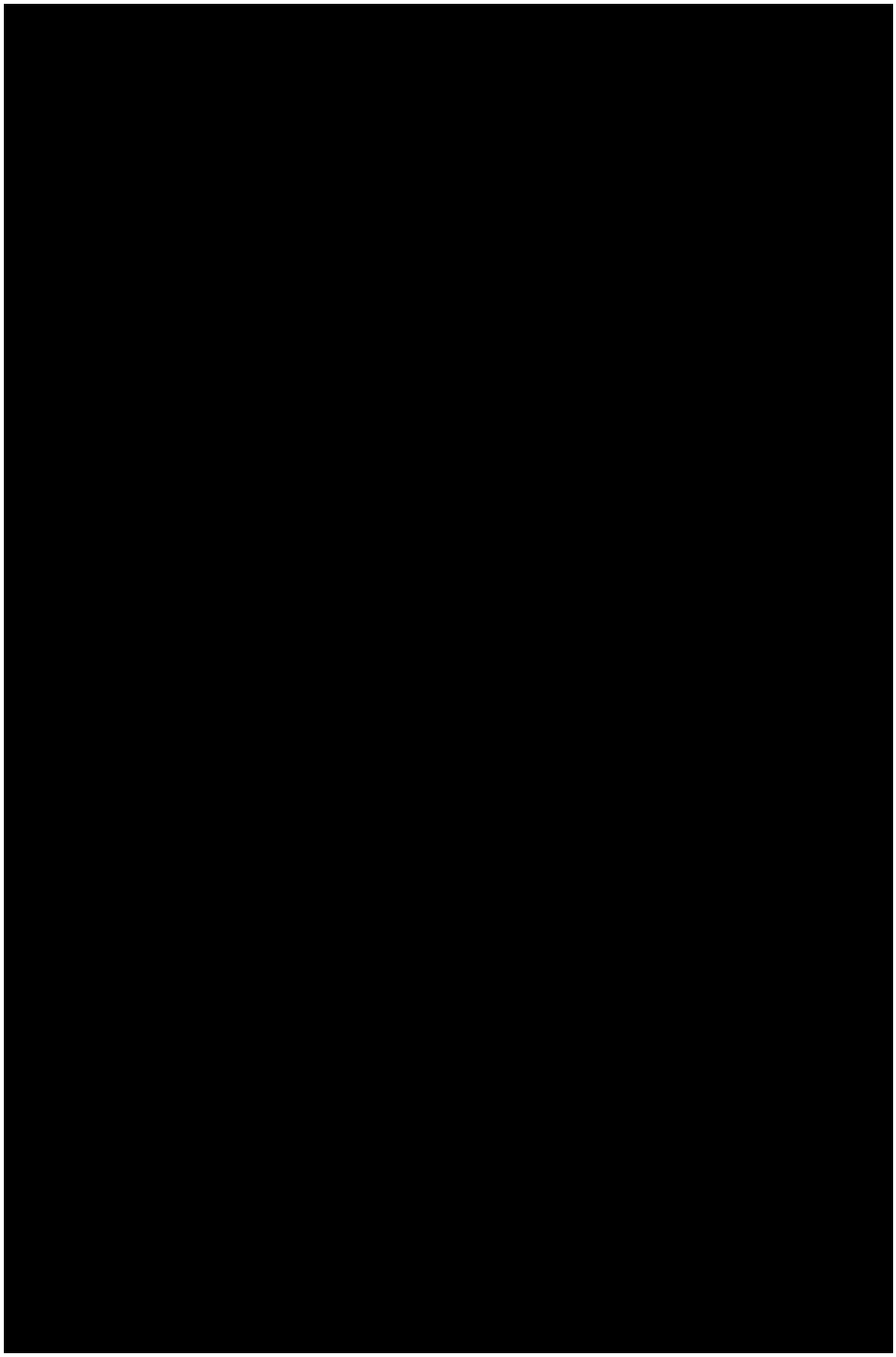
If the statement does not apply to you, circle N/A.

1. When all is said and done, I am the person who is responsible for taking care of my health	Disagree Strongly	Disagree	Agree	Agree Strongly	N/A
2. Taking an active role in my own health care is the most important thing that affects my health	Disagree Strongly	Disagree	Agree	Agree Strongly	N/A
3. I am confident I can help prevent or reduce problems associated with my health	Disagree Strongly	Disagree	Agree	Agree Strongly	N/A
4. I know what each of my prescribed medications do	Disagree Strongly	Disagree	Agree	Agree Strongly	N/A
5. I am confident that I can tell whether I need to go to the doctor or whether I can take care of a health problem myself	Disagree Strongly	Disagree	Agree	Agree Strongly	N/A
6. I am confident that I can tell a doctor concerns I have even when he or she does not ask	Disagree Strongly	Disagree	Agree	Agree Strongly	N/A
7. I am confident that I can follow through on medical treatments I may need to do at home	Disagree Strongly	Disagree	Agree	Agree Strongly	N/A
8. I understand my health problems and what causes them	Disagree Strongly	Disagree	Agree	Agree Strongly	N/A
9. I know what treatments are available for my health problems	Disagree Strongly	Disagree	Agree	Agree Strongly	N/A
10. I have been able to maintain (keep up with) lifestyle changes, like eating right or exercising	Disagree Strongly	Disagree	Agree	Agree Strongly	N/A
11. I know how to prevent problems with my health	Disagree Strongly	Disagree	Agree	Agree Strongly	N/A
12. I am confident I can figure out solutions when new problems arise with my health	Disagree Strongly	Disagree	Agree	Agree Strongly	N/A
13. I am confident that I can maintain lifestyle changes, like eating right and exercising, even during times of stress	Disagree Strongly	Disagree	Agree	Agree Strongly	N/A

3

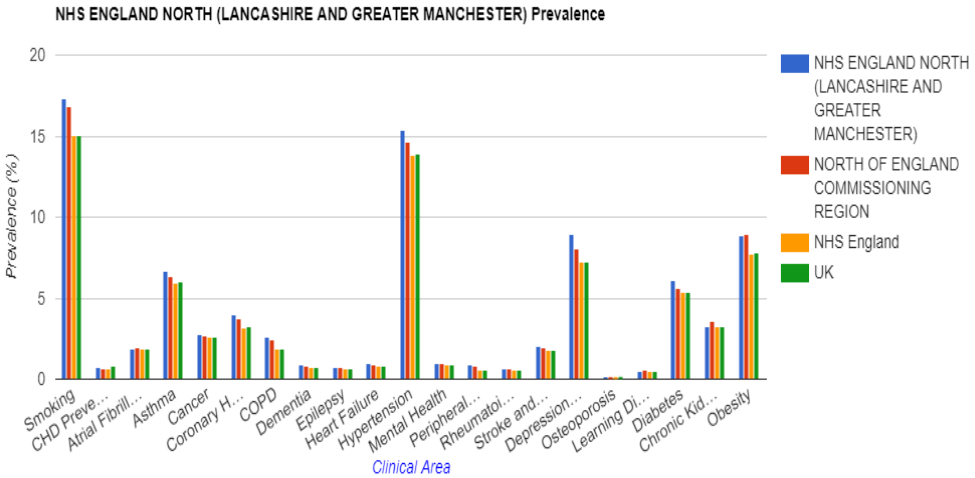
16.4 Appendix 4: [redacted]

[redacted]



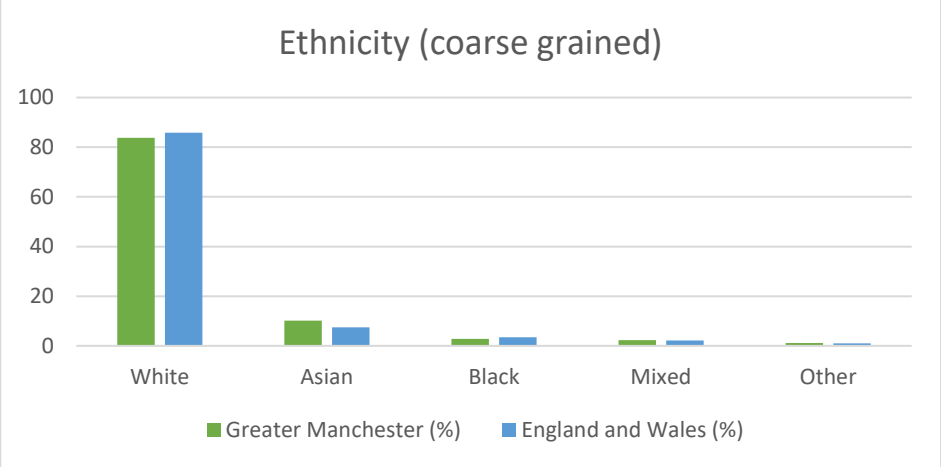
16.5 Appendix 5: Generalisability of the Greater Manchester Population to the UK

16.5.1 Key indicators of generalisability of the Greater Manchester population to the UK



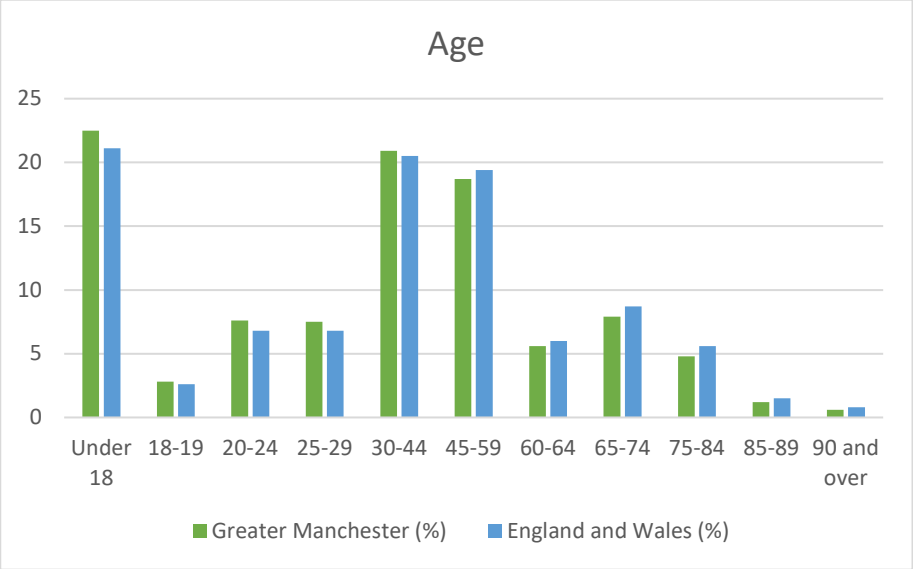
The Quality and Outcomes in Primary Healthcare (QOPH) demonstrate that chronic disease prevalence in Greater Manchester is comparable across the UK population as a whole (Quality and Outcomes in Primary Healthcare data, 2018).

16.5.2 Greater Manchester population by ethnicity, compared with England and Wales



The breakdown of the Greater Manchester population by ethnicity is very similar to that of England and Wales as a whole. Greater Manchester has a slightly higher Asian (Pakistani) population, a slightly lower White population and a slightly lower Black (Caribbean) population (Office of National Statistics Ethnic Group, 2011).

16.5.3 Greater Manchester population by Age, compared with England and Wales



The age distribution of the Greater Manchester population is almost identical to that of the England and Wales population. Contrast for example, Inner London where the proportion of 30-44-year olds can be as high as 30%, or local authorities on the South coast, where it can be as low as 14% (Office of National Statistics Age Group, 2011).

16.5.4 Greater Manchester male population, compared with England and Wales

The proportion of males in the Greater Manchester population, stratified by age, is very similar to that for the UK as a whole. The biggest difference, 1.1%, occurs in the 80-84 age group (Office of National Statistics Male Group, 2011).

16.6 Appendix 6: Calculating the 4-level Physical Activity Index (PAI)

The General Practice Physical Activity Questionnaire is intended for use in adults (16 – 74) years in routine general practice to provide a simple, 4-level Physical Activity Index (PAI) reflecting an individual's current physical activity. The index can be cross-referred to Read codes for physical activity and can be used to help inform the decision as to when interventions to increase physical activity might be appropriate.

Patients can be classified into four categories:

Inactive	• Sedentary job and no physical exercise or cycling
Moderately inactive	• Sedentary job and some but < 1 hour physical exercise and / or • cycling per week OR • Standing job and no physical exercise or cycling
Moderately active	• Sedentary job and 1-2.9 hours physical exercise and / or cycling per week OR • Standing job and some but < 1 hour physical exercise and / or cycling per week OR • Physical job and no physical exercise or cycling
Active	• Sedentary job and ≥ 3 hours physical exercise and / or cycling • per week OR • Standing job and 1-2.9 hours physical exercise and / or cycling per week OR • Physical job and some but < 1 hour physical exercise and / or cycling per week OR • Heavy manual job

Note: Questions concerning Walking, Housework/Childcare and Gardening/DIY have been included to allow patients to record their physical activity in these categories, however these questions have not been shown to yield data of a sufficient reliability to contribute to an understanding of overall physical activity levels. As noted above further questioning is required.

Summary of the PAI

	Occupation			
Physical exercise and / or cycling (hr/wk)	Sedentary	Standing	Physical	Heavy Manual
0	Inactive	Moderately Inactive	Moderately Active	Active
Some but < 1	Moderately Inactive	Moderately Active	Active	Active
1-2.9	Moderately Active	Active	Active	Active
≥ 3	Active	Active	Active	Active