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Protocol

Implementation of inclisiran in UK primary care for patients with atherosclerotic cardiovascular disease (ASCVD) or ASCVD-risk equivalents: rationale and design of VICTORION-Spirit, a pragmatic phase IIIb, randomised controlled study

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ABSTRACT

Background: Translational gaps exist in implementing health innovations rapidly in clinical practice. Pragmatic effectiveness and implementation studies, therefore, play a pivotal role in understanding how high-value health innovations could be deployed and delivered in healthcare systems to reduce barriers to adoption and provide more rapid patient benefit. VICTORION-Spirit is an ongoing pragmatic, 9-month, phase IIIb, open-label, multicentre, randomised controlled study evaluating the implementation, patient experience, and delivery of the subcutaneous lipid-lowering therapy, inclisiran sodium 300 mg, in participants with elevated low-density lipoprotein cholesterol (LDL-C) who are on established lipid-lowering medication, or have been recommended lipid-lowering therapy but are unable to tolerate treatment.
Methods: VICTORION-Spirit utilises a type 1 hybrid effectiveness-implementation design, where the primary objective is to demonstrate superiority of inclisiran with or without (±) behavioural support versus standard of care (SOC; e.g., statin and/or other lipid-lowering therapies) + behavioural support in terms of percentage reduction in LDL-C from baseline to Day 270 in a primary care setting. Secondary objectives will evaluate implementation of inclisiran ± behavioural support versus SOC + behavioural support through assessment of: patient satisfaction and patient activation/empowerment after treatment at Day 90; adherence to cardiovascular disease self-management; and serious adverse event profile. Additionally, a process evaluation ascertaining the views of: patients, providers, and National Health Service (NHS) commissioners will explore barriers and enablers to integrating inclisiran within primary care.
Conclusions: The results of VICTORION-Spirit have potential to change our approach to lipid management and inform further implementation efforts in healthcare systems, such as the NHS.
Trial registration: ClinicalTrials.gov NCT04807400.

Keywords: Implementation science, Primary care, Population health, Protocol, Cardiovascular disease, Inclisiran

INTRODUCTION

Translational gaps in implementing innovations rapidly in clinical practice present a challenge for healthcare systems globally. To overcome this hurdle in the UK, the Accelerated Access Collaborative, a partnership between industry, regulators, government bodies, patients, and the NHS, was established with the goal of fast-tracking the development of and access to high-value innovations - a goal that may be achieved using implementation science.[1]

Implementation science is the study of methods to promote the systematic uptake of proven clinical treatments and evidence-based practices into routine clinical practice, with the aim of ultimately improving the delivery of health services.[2] Implementation science typically focuses on interventions with established real-word effectiveness following marketing authorisation. However, understanding whether and how an innovation can be successfully implemented is not dependent on effectiveness first being established. Many questions relating to how best to implement an innovation in practice can be addressed concurrently with the assessment of effectiveness rather than sequentially. Doing so could accelerate the deployment of innovations and provide benefit to patients more broadly, rapidly, and equitably - VICTORION-Spirit (NCT04807400) is a study attempting to achieve this.

VICTORION-Spirit is a pragmatic phase IIIb implementation research study. The study is assessing how inclisiran, a lipid-lowering innovation that was first authorised in the UK in 2021, can be deployed and delivered in a healthcare system to treat appropriate patients (i.e., patients at risk of future cardiovascular events and not reaching LDL-C goals despite existing lipid-lowering therapies) at a population health level.[3]

Elevated LDL-C is a modifiable risk factor for atherosclerotic cardiovascular disease (ASCVD), a leading cause of death worldwide.[4,5] A meta-analysis of trials evaluating statin therapy (the current drug of choice for primary and secondary prevention of cardiovascular disease[6]) indicated that cardiovascular events are reduced by 20% for each 1 mmol/l reduction in LDL-C.[7] However, despite their proven efficacy, some patients are intolerant to statins, which may result in early treatment discontinuation,[8] and many patients are unable to reach LDL-C goals despite lipid-lowering therapy.[9] Previous phase III inclisiran trials, ORION-10 (NCT03399370) and ORION-11 (NCT03400800), were conducted in secondary care and demonstrated that inclisiran significantly reduced LDL-C levels in patients with ASCVD and ASCVD-risk equivalents, with a tolerable safety profile.[10] VICTORION-Spirit was started before the marketing authorisation of inclisiran and uses a type 1 hybrid effectiveness-implementation study design, an established implementation research approach that emerged to bridge the translational gap between clinical research discoveries and routine practice.

Type 1 study designs focus on evaluating a clinical innovation in a 'real-world' scenario to observe and gather information on implementability of the innovation, including barriers and enablers to implementation.[11] In VICTORION-Spirit, which uses a primary care model of delivery, the 'real-world' scenario includes a primary care setting to reflect where inclisiran would be implemented in practice. This ensures that enough patients can be reached to enable a population health approach, which would be challenging to achieve in secondary care alone. The patient population under study will be aligned with the inclisiran licensed indication, with the intention of working with a population that is likely to be affected by inclisiran in clinical practice and therefore likely to be of benefit to those patients. As such, the study aims to address health inequalities in cardiovascular research, aligning with the NHS England objective of 'levelling up'.

Here, we describe the protocol for VICTORION-Spirit, the first study of its kind to investigate effectiveness and evidence for the implementation of a lipid-lowering therapy within a primary care setting in the NHS to support population health management strategies.

METHODS

Study design

VICTORION-Spirit (NCT04807400) is a pragmatic, type 1 hybrid effectiveness–implementation research study, designed to test clinically relevant outcomes and explore the 'implementability' of an intervention. The pragmatic aspects of VICTORION-Spirit and the rationale for study design choices are summarised in Table 1 based on guidance by Loudon et al.[12] This 9-month, phase IIIb, open-label, multicentre, randomised controlled study will evaluate the implementation, patient experience, and delivery of inclisiran in participants with elevated LDL-C who are on established lipid-lowering medication, or have been recommended lipid-lowering therapy by their healthcare provider but are unable to tolerate treatment. This study is being conducted in accordance with the International Council for Harmonisation Harmonised Tripartite Guidelines for Good Clinical Practice, with applicable local regulations, and the ethical principles set forth in the Declaration of Helsinki. An independent ethics committee approved the study protocol, and all patients are required to provide written, informed consent prior to participation in study. As approved by the Medicines and Healthcare Products Regulatory Agency, a data monitoring committee will not be included in this trial, as inclisiran (a marketed medicine) will be used at the licensed dose.

Generalisability of the study population to the UK and maintenance of the pragmatic nature of VICTORION-Spirit are essential. The study will be performed in a primary care setting across Greater Manchester, UK and patients will be recruited by their general practitioner (GP). In total, 900 participants across 17 general practices in Greater Manchester will be required for this study. A list of the study sites can be found on clinicaltrials.gov.

Table 1: Pragmatic aspects of the VICTORION-Spirit study design.

Study design considerations	Rationale for study design choices in VICTORION-Spirit
Eligibility - How similar are participants in the study to those expected to receive the intervention in the real world?[12]	The VICTORION-Spirit inclusion and exclusion criteria reflect the licence of inclisiran to facilitate working with populations that will be affected by inclisiran rather than selecting patients who are eligible for standard clinical trials.
Recruitment - How are participants recruited into the study?[12]	FARSITE, a tool that utilises SNOMED clinical term codes for searching, finding, and contacting relevant patients with research opportunities, will be used to optimise patient identification and recruitment at participating GP practices. GPs will manually confirm if their patients meet the protocol eligibility criteria and decide if they should be contacted.
Setting - How different is the setting of the study from usual care?[12]	A pragmatic study design will be employed – the study will be executed in a primary care setting where inclisiran is intended to be implemented in clinical practice. The study also consists of broad inclusion criteria and few exclusion criteria.
Organisation - What expertise and resources are required to deliver the intervention?[12]	Inclisiran will be administered by a GP or practice nurse/pharmacist to reflect clinical practice. Behavioural support (telephone-based lifestyle intervention) will be provided by non-clinical health advisors trained in motivational interviewing and coaching techniques to motivate and support patients to make effective choices for improving self-management.
Delivery - Is there flexibility in the delivery of the intervention?[12]	Minimal intervention will be required. The inclisiran dosing regimen (inclisiran sodium 300 mg on day 1 and day 90) used in the study is in line with the licence. Usual treatment will be permitted - all participants will continue to receive SOC lipid-lowering background therapy throughout the study; the background therapy and dose are determined by participants' treating clinicians. Minimal review will be required as most data will be captured using EMRs. The behavioural support programme will be standardised in that all patients will receive the same number of calls; however, it will be flexible in that the focus and content of calls will be tailored to the needs of the individual.
Adherence - What measures are in place to ensure patients adhere to study intervention(s)?[12]	Adherence to treatment will be evaluated through analysis of medications dispensed (for SOC) and administered (for inclisiran treatment). Participants in the inclisiran treatment groups will be reminded to be available for each administration of inclisiran by a qualified clinical staff; these participants may also receive SMS text reminders from their GP practice, which is common in clinical practice.
Follow-up - How closely are participants followed up?[12]	Percentage reduction in LDL-C from baseline to Day 270, where maximal lipid lowering is expected, will be evaluated. Patient satisfaction, patient activation and empowerment, and adherence to treatment will be evaluated after treatment on day 90. ConneXon will be used for remote safety monitoring in 'real time' to minimise direct contact with patients and maintain 'real-world' conditions for patients.
Primary objective - How relevant is the primary objective to participants?[12]	Lowering LDL-C is expected to improve cardiovascular outcomes in patients with ASCVD and ASCVD-risk equivalents. The primary objective of VICTORION-Spirit is to demonstrate superiority of inclisiran with or without behavioural support compared with SOC with behavioural support on LDL-C reduction from baseline to day 270 in a primary care setting; this will enable assessment of whether the benefits of inclisiran demonstrated in previous ORION studies can be reproduced within a primary care setting, where inclisiran is intended to be implemented.
Primary analysis - To what extent will all available data be included in the primary analysis?[12]	The intention-to-treat principle will be applied. All patients who are randomised and receive at least one dose of study treatment will be included in the analyses of primary, secondary, and exploratory objectives. Multiple imputation will be used to impute missing data.

ASCVD-atherosclerotic cardiovascular disease; EMR-electronic medical record; GP-general practitioner; LDL-C-low-density lipoprotein cholesterol; SMS-short message service; SNOMED-Systematized Nomenclature of Medicine; SOC-standard of care.

The assessment schedule that will be used in VICTORION-Spirit is outlined in Figure 1. As lipid management should be accompanied by dietary and lifestyle intervention, standard of care (SOC) for lipid management plus access to behavioural support was chosen as the comparator group in VICTORION-Spirit. At screening, eligible patients will be randomised 1:1:1 via interactive response technology to one of the three treatment groups: (1) SOC therapy and behavioural support, where participants will continue to receive their background lipid-lowering therapy, such as statin and/or ezetimibe, and will be provided with access to a behavioural support service; (2) SOC therapy and inclisiran, where participants will continue to receive their background lipid-lowering therapy plus subcutaneous inclisiran sodium 300 mg; or (3) SOC therapy, inclisiran, and behavioural support, where participants will continue to receive their background lipid-lowering therapy plus subcutaneous inclisiran sodium 300 mg, with access to a behavioural support service (Figure 2).

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)
Informed consent	X			
Demography	X			
Inclusion/exclusion criteria	X			
Relevant/current medical history[a]	→	→	→	→
Height	X			X
Weight	X			X
BMI	X			X
Smoking status	X			X
Dietary advice status	X			X
Exercise status	X			X
Vital signs - blood pressure	X			X
HbA1C[b]	X			X
Lipid profile/biomarkers[c]	X		X	X
Urine pregnancy test for WOCBP	X			
Adverse events[d]	X	→	→	→
Prior/concomitant medications[a]	→	→	→	→
Patient-reported outcomes (PAM)[e]	X		X	
Patient-reported outcomes (CSQ-8)[e]			X	
Bespoke patient assessment questionnaire[e]			X	X
Behavioural support programme[f]		Participants in the inclisiran plus behavioural support and SOC plus behavioural support arms will have access to this service throughout the study		
Process evaluation[g]		→	→	→
Healthcare resource utilisation[a]	→	→	→	→
Study drug administration		X	X	
IWRS/IRT registration/randomisation	X	X	X	X

Figure 1: Assessment schedule in VICTORION-Spirit.

BMI-body mass index; CSQ-8-Client satisfaction questionnaire; eCRF-electronic case report form; EMR-electronic medical record; IWRS-Interactive web response system; IRT-interactive response technology; HbA1C-haemoglobin A1C; PAM-Patient activation measure; SOC-standard of care; WOCBP-women of childbearing potential.

[a]ConneXon will automate regular collection from EMR.

[b]ConneXon will automate collection of closest recorded value prior to the screening/baseline visit and end of study visit.

[c]Capillary sample to be taken for immediate analysis using a CardioChek device for analysis of lipid profile.

[d]After screening/baseline visit, all serious adverse events will be monitored and collected using ConneXon.

[e]Patients will take questionnaires to complete after study visit and will return them by post, after which they will be transcribed by the study team into the eCRF.

[f]The behavioural support programme consists of a telephone-based support service, providing advice on diet, lifestyle, medication adherence, and cardiovascular risk management.

[g]Process evaluation interviews will be triggered by the study visits at day 1 and day 90.

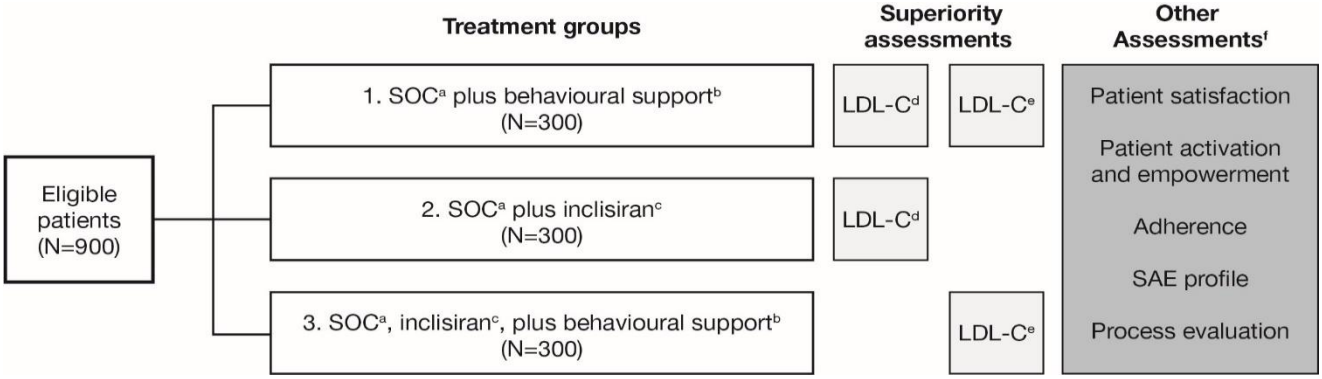

Figure 2: VICTORION-Spirit study design.

LDL-C-low-density lipoprotein cholesterol; NHS-National Health Service; SAE-serious adverse event; SOC-standard of care.
[a]Participants will receive SOC (statin and/or other lipid-lowering therapies) as background therapy.
[b]The behavioural support service provided to participants will consist of a monthly telephone-based lifestyle intervention to motivate and support patients to make effective choices for improving self-management through behaviour change, goal setting, and empowerment.
[c]Subcutaneous inclisiran sodium 300 mg.
[d]The superiority of inclisiran without behavioural support (treatment group 2) compared with SOC with behavioural support (treatment group 1) on percentage reduction in LDL-C from baseline to day 270 in a primary care setting will be assessed.
[e]The superiority of inclisiran with behavioural support (treatment group 3) compared with SOC with behavioural support (treatment group 1) on percentage reduction in LDL-C from baseline to day 270 in a primary care setting will be assessed.
[f]Other assessments will include: patient satisfaction with the services they have received or are currently receiving; patient activation and empowerment to evaluate the confidence of patients in managing their own health; adherence to treatment; SAE profile; and AEs leading to treatment discontinuation. A process evaluation to ascertain the views of patients and providers about the service they have received or provided and its potential transactability across the NHS will also be performed.

The behavioural support service provided to participants in treatment groups 1 and 3 will consist of a telephone-based, lifestyle intervention and will be delivered by health advisors trained in motivational interviewing and coaching techniques. The behavioural support provides education about lipids, diet, and other lifestyle factors. The intervention consists of: an introductory telephone call; an action planning call, lasting around 1 hour; provision of British Heart Foundation leaflets; and eight follow-up calls of around 40 minutes, delivered over 8 months. The first call focuses on lipids and diet, and subsequent calls are tailored to the needs of the individual participant. The health advisors signpost and refer participants to relevant local services, such as 'Healthy Heart Club' and local gyms. Participants also have access to specialists, such as a dietician and cardiologist, and can seek advice from them as needed. Participants in treatment groups 2 and 3 will be reminded to attend or be available for each administration of inclisiran by a qualified clinical staff; these participants may also receive short message service (SMS) text reminders from their general practice, which is common in clinical practice.

Previous studies have shown that inclisiran sodium 300 mg/1.5 ml (equivalent to 284 mg inclisiran) is well tolerated and provides maximum efficacy in LDL-C lowering, supporting the licensed dose of inclisiran for adults with hypercholesterolaemia or mixed dyslipidaemia.[13] In VICTORION-Spirit, a 300 mg dose of inclisiran sodium will be administered on day 1 and day 90 to all participants receiving inclisiran (Figures 1 and 2) to evaluate the superiority of inclisiran compared with SOC with behavioural support on percentage change in LDL-C from baseline to day 270, where maximal lipid lowering would be expected based on previous phase III studies.

Eligibility criteria

Inclusion and exclusion criteria can be found on clinicaltrials.gov (NCT04087400) and are in line with the licence of inclisiran, with the intention of working with populations that will be treated with inclisiran, rather than selecting patients who are suitable for a standard clinical trial.

Briefly, eligibility criteria include participants: (i) aged ≥18 years; (ii) on established lipid-lowering medication, or who have been recommended lipid-lowering therapy by their healthcare provider but are unable to tolerate treatment; (iii) with a total cholesterol level ≥4 mmol/l at screening; and (iv) on a stable dose of lipid-lowering therapy, such as statin and/or ezetimibe, for ≥30 days before screening with no planned medication/dose change.

Exclusion criteria include: (i) patients with previous exposure to inclisiran; (ii) a triglyceride measurement ≥4.52 mmol/l at screening; (iii) previous, current, or planned treatment with a monoclonal antibody targeting proprotein convertase subtilisin/kexin type 9 (PCSK9); and (iv) other factors which may limit the ability of patients to participate in the study or compromise their safety, such as surgical history.

Patient identification

VICTORION-Spirit will be conducted in general practices across Greater Manchester with a network of research-ready GPs. A proven system developed by NorthWest EHealth (NWEH), FARSITE, will be used to optimise patient identification and recruitment at participating GP practices. FARSITE is a tool that utilises electronic medical records (EMRs) and both Read/CTV3 and Systematized Nomenclature of Medicine (SNOMED) clinical term codes for searching, finding, and contacting relevant patients with research opportunities via their GP. FARSITE maintains patient confidentiality by anonymising information provided to researchers and only permitting GPs to decide if their patient should be contacted with research opportunities. Information about individuals who meet the study protocol eligibility criteria is only available to the GP; researchers do not have access to individual patient records. Once a list of potential participants has been identified using this tool, GPs will review the medical records of their patients manually to confirm their eligibility for participation based on the VICTORION-Spirit inclusion and exclusion criteria. An overview of patient identification using FARSITE in VICTORION-Spirit is provided by Gibson et al (Manuscript in preparation).

Primary objectives

The primary objective of VICTORION-Spirit is to demonstrate the superiority of inclisiran with or without behavioural support compared with SOC with behavioural support in terms of percentage reduction in LDL-C from baseline to day 270 in adults with elevated LDL-C in a primary care setting. This will enable testing of whether the benefits of inclisiran demonstrated in previous ORION studies can be reproduced in a pragmatic sample of primary care patients and will help assure decision-makers that the benefits of inclisiran can be achieved in a large, unselected population of primary care patients in the NHS.

Table 2: Description of PROMS (CSQ-8 and PAM) and bespoke questionnaires used in VICTORION-Spirit.

Questionnaire	Description
CSQ-8[14]	A validated 8-item survey to assess patient satisfaction with services they have received or are currently receiving. Response to each item is based on a 4-point scale. The directionality of response options span from very positive to very negative, and the order in which responses are presented is reversed randomly (from high to low, or low to high) from item to item to minimise stereotypic responses. All item responses will be summed to produce a total score, ranging from 8 to 32, with higher scores indicating higher satisfaction.
PAM[15]	A validated 13-item survey used to assess patients' knowledge, skills, and confidence in managing their own health. Consists of 13 statements; patients will be required to indicate how much they agree or disagree with each statement on a scale of 1-4, where 1 and 4 represent "strongly disagree" and "strongly agree", respectively. Patients may also answer "non-applicable", which is scored as 0. A calibration table will be used to score the PAM, with higher scores indicating that the patient is more activated; PAM scores will be categorised into four levels for descriptive purposes: Level 1 (scores <47.1): disengaged and overwhelmed; Level 2 (scores 47.1-53.2): become aware but still struggling; Level 3 (scores 53.2-70.2): taking actions; Level 4 (scores >70.2): maintaining behaviours and pushing further.
Bespoke	Used to assess treatment simplicity, burden, and impact. The bespoke patient-reported experience questionnaire is informed by existing validated PROMS questionnaires (RetTSQ and DTSQ) and has been co-produced with patient and public contributors registered with Research for the Future (an NIHR Clinical Research Network Initiative).[29-31]

CSQ-8-Client satisfaction questionnaire; DTSQ-Diabetes treatment satisfaction questionnaire; NIHR-National Institute for Health and Care Research; PAM-Patient activation measure; PROMS-Patient-reported outcome measures; RetTSQ-Retinopathy treatment satisfaction questionnaire.

Secondary objectives

Secondary objectives will evaluate the implementation of inclisiran with or without behavioural support compared with SOC with behavioural support in a primary care setting using the following assessments: (i) Measures of patient satisfaction using the validated client satisfaction questionnaire-8 (CSQ-8) patient-reported outcome measures (PROMs) questionnaire (Table 2) after treatment at day 90.[14] (ii) Measures of patient activation and empowerment using the validated 13-point patient activation measure (PAM) PROMs questionnaire (Table 2) at baseline and after treatment at day 90.[15] (iii) Assessment of medication adherence during the study period based on analysis of medications dispensed (for SOC) and administered (for inclisiran treatment).

(iv) A theory-driven process evaluation to explore: the barriers and enablers to integrating inclisiran delivery within primary care; the views and experiences of those delivering and receiving inclisiran; the acceptability and sustainability of patient identification and referral routes; and the 'core enabling ingredients' necessary to support the wider delivery of inclisiran within the NHS. (v) Serious adverse event (SAE) profile and adverse events (AEs) leading to treatment discontinuation.

Process evaluation

The process evaluation will be informed by the consolidated framework for implementation research (CFIR). The CFIR is shaped by diffusion of innovations theory that seeks to explain how, why, and at what rate innovations spread through social systems.[16] It is widely used in implementation research to guide systematic assessment of factors that influence the adoption of implementation strategies and will be used in VICTORION-Spirit to identify what is needed to support the implementation of inclisiran in the real world.[17,18] Using a determinants framework like CFIR provides a systematic basis for capturing and analysing different stakeholder views on acceptability, feasibility, and the sustainability of implementation processes. This information can then be used to inform decisions on wider use adoption and spread.

Interviews with patients, providers, NHS commissioners, and representatives from the Academic Health Science Network (AHSN) will be conducted. This will consist of semi-structured telephone interviews with a purposive sample of patients, practice nurses, pharmacists, GPs, and practice managers drawn from the participating practice sites. In addition, telephone interviews will be conducted with NHS commissioners and AHSN representatives to explore the wider 'transactability' of inclisiran delivery beyond the auspices of the trial setting.

Telephone interviews will be arranged at a day/time suitable for the respondent. Topic guides informed by the CFIR (and PROMs questionnaires for the patient participants) will be used to explore feasibility and acceptability from a range of perspectives. Interviews will cover access, acceptability, and feasibility of implementing the process of care necessary for 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.

Interviews will be audio-recorded with consent, transcribed, and thematically analysed using a modified framework approach; NVivo software will be used to manage the data. This will produce a matrix of summarised data, providing a structure for analysis and interpretation.[19] This approach will enable the researchers to answer the specific research questions that have been set, whilst allowing important insights to be produced inductively. Of note, the modified framework approach will utilise the strengths of framework analysis in providing structure to the analysis of large datasets and facilitating comparisons between different participant groups on key issues. Subsequent theme refinement will be deductive and guided by the CFIR. This will enable the researchers to produce a matrix of summarised data, providing a structure for the analysis.

Exploratory objectives

Exploratory objectives will compare inclisiran with or without behavioural support to SOC with behavioural support in a primary care setting on the following assessments: (i) total lipid profile, blood pressure, weight, and body mass index (BMI) from baseline to end of study visit; (ii) healthcare resource utilisation during the study period taken from the primary and secondary care EMRs; and (iii) assessments of treatment simplicity, burden, and impact using validated and bespoke questionnaires (Table 2).

Safety

In VICTORION-Spirit, only SAEs will be detected, documented, and reported; AEs leading to treatment discontinuation will also be documented. The investigator or delegate is responsible for identifying and reporting events that meet these criteria and assessing AE severity and causality to the study treatment. Using NWEH's ConneXon trials platform, which utilises EMRs for remote safety monitoring of participants in 'real time', all hospital admissions and SAEs occurring after participants have provided informed consent until 30 days after the last study visit will be alerted to the study team and reported to the trial sponsor within 24 hours of awareness. Using this technology allows for remote safety monitoring with minimal intervention, thereby reducing patient visits and maintaining the 'real-world' conditions for the study. This novel safety monitoring is also capable of detecting a higher rate of SAEs compared with traditional trial methods for collecting safety information.[20] AEs may also be detected when they are volunteered by participants (e.g., during or between visits or other assessments, such as through PROMs questionnaires).

Statistical analysis

The study has been powered to detect treatment group differences equivalent to a Cohen's effect size of 0.3. Assuming a 20% dropout rate, a sample size of 300 patients per treatment group (900 patients in total) would be sufficient to detect this effect size with 90% power using a one-sided significance level of 0.025. This sample size could also detect a reduction of ≥10% change in LDL-C from baseline in the inclisiran group compared with the SOC group, assuming a standard deviation of 30% in the SOC group and 20% in the inclisiran group based on observed results from previous inclisiran studies.[10]

For the primary objective, an analysis of covariance (ANCOVA) model will be used to test the superiority of inclisiran with or without behavioural support over SOC therapy and behavioural support on the percentage change in LDL-C from baseline to day 270. 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. The washout model will assume that missing day 270 data are not missing at random in participants in the inclisiran groups who: (i) discontinue study treatment before the day 270 visit, or (ii) cannot be followed for scheduled LDL-C assessments. Missing data for participants in the SOC therapy and behavioural support group who discontinue prematurely will be imputed using the missing at random assumption. An ANCOVA model will be fitted to each imputed dataset, and the results will be combined using Rubin's combination rules. The difference in least-square means between treatment groups and corresponding 2-sided 95% confidence intervals will be calculated, and the Holm procedure will be used to control for the family-wise error rate for comparison of the two inclisiran groups with the SOC therapy and behavioural support group.

Secondary objectives will be analysed as follows: (i) Mean difference in CSQ-8 total score after treatment at day 90 between treatment groups will be analysed using analysis of variance (ANOVA). The mean difference, 95% confidence interval, and p value will be reported. (ii) Mean difference in PAM questionnaire total score will be analysed using an ANCOVA model. The model will include fixed effects of treatment group with baseline total scores as a covariate. The mean difference, 95% confidence interval, and p value will be reported. (iii) Adherence to cardiovascular disease self-management will be summarised by providing the frequency and percentages of patients in the four levels of the PAM scores (Table 2) by visit and treatment. (iv) SAEs and AEs leading to treatment discontinuation will be summarised by treatment. The methodology that will be adopted for analysis of the process evaluation portion of VICTORION-Spirit is described in the 'process evaluation' section.

DISCUSSION

Cardiovascular disease places a major burden on the NHS and is identified as "the single biggest condition where lives can be saved by the NHS over the next 10 years" within the NHS long-term plan.[21,22] VICTORION-Spirit is the first phase IIIb implementation research study in patients on established lipid-lowering therapies assessing how inclisiran can be deployed and delivered sustainably in a healthcare system at a population health level. The study, therefore, has the potential to inform primary care implementation of inclisiran in the NICE-endorsed lipid management pathway, a national lipid management guideline for primary and secondary prevention of cardiovascular disease.[6]

Various features of the VICTORION-Spirit study design are noteworthy. Firstly, the study is being conducted within the NHS in a primary care setting, where inclisiran is intended to be implemented in clinical practice. Secondly, the study population consists of patients on established lipid-lowering therapy, or who have been recommended lipid-lowering therapy but are unable to tolerate treatment, to reflect the licensed population for inclisiran. In addition, the NHS provides an ideal framework for assessing implementation strategies of novel health innovations, primarily due to its clear commissioning processes, robust EMRs, primary care-focused approach to managing patients with chronic disease, and goals within the NHS long-term plan of optimising service delivery to patients within their region. Furthermore, Greater Manchester, where the study is being conducted, presents an ideal population for testing population health approaches that employ a primary care model of delivery. This is due to generalisability of the Greater Manchester population to the wider UK population, the cohesion of primary and secondary care EMRs in Greater Manchester, the established use of implementation science approaches to assess new innovations in Greater Manchester, and their established primary care networks.[23] Lastly, various stakeholders, such as NHS commissioners, regional/national policymakers and clinicians, will be involved in the study and their viewpoints evaluated to explore what is needed to support implementation of inclisiran in the real world and inform future implementation efforts in the NHS and beyond.

Three types of effectiveness-implementation hybrid study designs have been described in the literature by Curran et al, namely type 1, type 2, and type 3.[11] Type 1 effectiveness–implementation hybrid study designs primarily involve evaluating the effectiveness of a clinical innovation while secondarily observing and gathering information on its delivery and/or potential 'implementability' in a 'real-world' scenario. VICTORION-Spirit utilises a type 1 hybrid design as the efficacy of inclisiran has not previously been established in a primary care setting or beyond phase III clinical trials. The chosen type 1 hybrid design, therefore, facilitates assessment of the effectiveness of inclisiran in a 'real-world' scenario (primary care) and is valuable for supporting inclisiran implementation strategies.

Evidence of the efficacy and safety of innovations is typically required for regulatory approval and supporting clinical decisions. Pragmatic study designs are appealing in the evidence-generation pathway for numerous reasons. Firstly, explanatory randomised controlled trials, which are typically used to generate evidence of the clinical safety and efficacy of an intervention, are highly controlled and enrol a selected patient population compared with the real-world population expected to be prescribed an intervention following regulatory approval. In addition, explanatory randomised controlled trials can be poor predictors of real-world effectiveness as interventions are typically tested in idealised conditions and populations, whereas pragmatic trials attempt to

mirror the conditions of routine practice. There are also challenges in measuring the impact of interventions on patient healthcare-seeking behaviour and utilisation of healthcare services in clinical trials with defined visits and procedures, dictated by a prescriptive trial protocol rather than typical clinical practice. Furthermore, there is a need to understand how and why innovations are successfully implemented in some settings, but not others, to inform implementation efforts. Of note, the pragmatic, type 1 hybrid study design utilised in VICTORION-Spirit aims to minimise the burden of clinical trial participation on patients and healthcare providers and mimic real-world delivery of healthcare as closely as possible. This will be facilitated using NWEH's bespoke ConneXon system. ConneXon is a unique and validated clinical trial platform built upon the technology and expertise developed for delivery of the Salford Lung Study, a pre-registration pragmatic trial in patients with asthma.[24] It integrates patient-level EMR data from primary care, secondary care, pharmacy, and other available national data sources to help generate 'real-world' evidence of the impact of inclisiran on individually consented participants. As most data in VICTORION-Spirit will be collected from patients' EMRs, there will be minimal direct contact with participants to maximise focus on outcomes of interest related to implementation. In addition, the integration of various healthcare data sources may provide more comprehensive safety information than usually obtained in traditional randomised controlled trials.[25]

Limitations

The VICTORION-Spirit study design has limitations. Firstly, health inequalities remain a challenge in research and may influence which patient groups agree to participate in studies. Secondly, although the length of follow-up (270 days) in the study is adequate for evaluating LDL-C changes, it is inadequate for detecting differences in long-term health outcomes. Additionally, only one region (Greater Manchester) has been used to inform implementation strategies nationally; nonetheless, it should be acknowledged that the Greater Manchester population is comparable to the wider UK population in terms of key indications, such as ethnicity, age distribution, sex (stratified by age), and prevalence of chronic disease.[26-28]

CONCLUSION

In summary, VICTORION-Spirit is an innovative study evaluating the implementation of inclisiran in UK primary care for patients with ASCVD or ASCVD-risk equivalents. The study may change our approach to lipid management, as well as inform future implementation efforts in healthcare systems such as the NHS.

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