potential patients as site staff will be part of their usual care teams. The patient information sheet will describe the study including any risks and potential benefits of enrolling. Written informed consent will be obtained from the patient prior to commencing any research procedures.
Patients will be given an adequate amount of time to consider their participation in the trial. If the patient agrees to participate in the trial they will be asked to sign the Informed Consent Form which will then be countersigned by the responsible clinician / researcher. The patient will retain one copy of the signed Consent Form. Another copy will be placed in the patient's medical records whilst the original will be retained in the research record for the patient at sites.
The right of the participant to refuse to participate without giving reasons must be respected. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

9.10 Participant Confidentiality

The investigator must ensure that the participant's confidentiality is maintained. On the eCRF or other documents submitted to the Sponsors, participants will be identified by a participant ID number only. Documents that are not submitted to the Sponsor (e.g., signed informed consent form) should be kept in a strictly confidential file by the investigator.

The investigator shall permit direct access to participants' records and source document for the purposes of monitoring, auditing, or inspection by the Sponsor, authorised representatives of the Sponsor, NHS, Regulatory Authorities and RECs.

9.11 Data Protection and Participant Confidentiality

The investigators and study site staff will comply with the requirements of the Data Protection Act 2018 concerning the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

9.12 End of Trial

End of Trial will be when all study visits are complete, all data are captured on the database and the study database is declared clean and hard-locked.

9.13 Study Documentation and Data Storage

The investigator must retain essential documents until notified by the Sponsor, and for at least ten years after study completion. Participant files and other source data (including copies of protocols, CRFs, original reports of test results, correspondence, records of informed consent, and other documents pertaining to the conduct of the study) must be retained. Documents should be stored in such a way that they can be accessed/data retrieved at a later date. Consideration should be given to security and environmental risks.

No study document will be destroyed without prior written agreement between the Sponsor and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, written agreement must be obtained from the Sponsor.

10. DATA MANAGEMENT

10.1 Source Data

Source documents include original documents related to the trial - including participant medical history and participant medical treatment. Source documentation must be maintained to allow reliable verification and validation of the trial data. Source data for this trial will be defined in the Monitoring Plan.

10.2 Language

CRFs will be in English. Generic names for concomitant medications should be recorded in the CRF wherever possible. All written material to be used by participants must use vocabulary that is clearly understood, and be in the language appropriate for the study site in the UK, Spain and Italy.

10.3 Database

The trial data will be collected on an electronic case report form (eCRF). The principal means of data collection from participant visits will be Electronic Data Capture (EDC) via the internet using the OpenClinica database. Data is entered into the EDC system by trained site personnel. All data recorded in the eCRF will be signed off by the Investigator or his/her appropriate designee. All changes made following initial submission of data will have an electronic audit trail with a date. Specific instructions and further details will be outlined in the study specific eCRF manual.

10.4 Data Collection

Details of procedures for CRF/eCRF completion will be provided in a study manual.

10.5 Archiving

All trial documentation, including that held at participating sites and the trial coordinating centre, will be archived for a minimum of 10 years following the end of the study. All investigational sites will be responsible for archiving all trial documentation.

11. STUDY MANAGEMENT STRUCTURE

11.1 Trial Executive Committee

A Trial Executive Committee (TEC) will be convened including as a minimum an independent clinician, the Chief Investigator, National Leads and other international experts in the field. The role of this committee is to provide overall supervision of trial progress.

11.2 Early Discontinuation of the Study

In case of early discontinuation of the study, the Follow-up Visit assessments should be performed for each participant, as far as possible.

11.3 Risk Assessment

A study-specific risk assessment will be performed prior to the start of the trial to assign a risk category of 'low', 'medium' or 'high' to the trial. Risk assessment will be carried out by the ICTU QA Manager in collaboration with the Study/ Operations Manager and the result will be used to guide the monitoring plan. The risk assessment will consider all aspects of the trial and will be updated as required during the course of the study.

11.4 Monitoring

The study will be monitored periodically by trial monitors to assess the progress of the study, verify adherence to the protocol, ICH GCP E6 guidelines and other national/international requirements and to review the completeness, accuracy and consistency of the data.

Monitoring procedures and requirements will be documented in a Monitoring Plan, in accordance with the risk assessment.

11.6 Quality Control and Quality Assurance

Quality Control will be performed according to ICTU internal procedures. The trial may be audited by a Quality Assurance representative of the Sponsor and/or ICTU. All necessary data and documents will be made available for inspection.

The study may be subject to inspection and audit by regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd Edition).

11.6 Peer review

The trial has been reviewed by senior members of ICTU and researchers at Imperial College London, as well as two independent peer reviewers.

11.7 Publication and Dissemination policy

Results will be presented at national and international scientific meetings to both cardiovascular and general physicians. All results will be published in high impact, general medical journals using open access policies and will be prepared in accordance with the internationally recognised standards for the publication of scientific results in peer-reviewed journals. We will communicate the results to the general public, we will also use appropriate media channels via Imperial College Public Relations team to disseminate results. All participating sites will be informed of the results and encouraged to disseminate findings via their own institutional social media platforms and patient and public engagement groups.

Information concerning the trial, patent applications, processes, scientific data or other pertinent information is confidential and remains the property of the Sponsor. The investigator may use this information for the purposes of the study only.

It is understood by the investigator that the Sponsor will use information developed in this clinical study and, therefore, may disclose it as required to other clinical investigators. In order to allow the use of the information derived from this clinical study, the investigator understands that he/she has an obligation to provide complete test results and all data developed during this study to the Sponsor.

Verbal or written discussion of results prior to study completion and full reporting should only be undertaken with written consent from the Sponsor.

Therefore all information obtained as a result of the study will be regarded as CONFIDENTIAL, at least until appropriate analysis and review by the investigator(s) are completed.

The results may be published or presented by the investigator(s), but the Sponsor will be given the opportunity to review and comment on any such results for up to 1 month before any presentations or publications are produced.

A Clinical Study Report summarising the study results will be prepared and submitted to the REC within 90 days of the end of study.

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13. REVISION HISTORY

Version	Date	Summary of changes
1.0	04/OCT/2022	First version
2.0	17/FEB/2023	Minor updates to software details Several minor administrative updates
3.0	17/JAN/2024	Addition of EU Representative Update to Endpoints Update to References (no. 24 + 26) Funder legal name change/ other administrative & staffing updates

SIGNATURE PAGE 1 (CHIEF INVESTIGATOR)

The signature below constitutes approval of this protocol by the signatory, on behalf of the Protocol Development Group, and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol including all statements regarding confidentiality.

Study Title: Implementation of a Decision Support System and its effect on early optimisation of Lipid-Lowering Therapies in patients with Acute Coronary Syndrome: a cluster Randomised Controlled Trial

Protocol Number:

Signed: Kausik Ray Digitally signed by Kausik Ray Date: 2024.01.23 13:32:24 Z

_____

Professor Kausik K Ray

Date: _____

SIGNATURE PAGE 2 (SPONSOR)

The signatures below constitute approval of this protocol by the signatory.

Study Title: Implementation of a Decision Support System and its effect on early optimisation of Lipid-Lowering Therapies in patients with Acute Coronary Syndrome: a cluster Randomised Controlled Trial

Protocol Number:

Signed: Becky Ward Digitally signed by Becky Ward Date: 2024.01.23 11:05:13 Z

Becky Ward
Research Governance and Integrity Manager
Research Governance and Integrity Team

Date: _____

SIGNATURE PAGE 3 (STATISTICIAN)

The signatures below constitute approval of this protocol by the signatory.

Study Title: Implementation of a Decision Support System and its effect on early optimisation of Lipid-Lowering Therapies in patients with Acute Coronary Syndrome: a cluster Randomised Controlled Trial

Protocol Number:

Signed: Professor Victoria Cornelius Digitally signed by Professor Victoria Cornelius Date: 2024.01.23 14:19:26 Z

_____

Professor Victoria Cornelius

Imperial Clinical Trials Unit

Date: _____

SIGNATURE PAGE 4 (PRINCIPAL INVESTIGATOR)

The signature of the below constitutes agreement of this protocol by the signatory and provides the necessary assurance that this study will be conducted at his/her investigational site according to all stipulations of the protocol including all statements regarding confidentiality.

Study Title: Implementation of a Decision Support System and its effect on early optimisation of Lipid-Lowering Therapies in patients with Acute Coronary Syndrome: a cluster Randomised Controlled Trial

Protocol Number:

Address of Institution: _____

_____

_____

Signed: _____

Print Name and Title: _____

Date: _____

14.APPENDICES

14.1 Sample GP Letter

Study Letter: Implementation of a Decision Support System and its effect on early optimisation of Lipid-Lowering Therapies in patients with Acute Coronary Syndrome: a cluster Randomised Controlled Trial

(insert date)
Dr. (insert GP name)
(insert GP address and contact details)

Dear Dr. (insert GP name),
Participant Name:
DOB:
Address:
RE: OptimiZation Of lipid lowering therapies using a Decision support system In patients with Acute Coronary syndrome (ZODIAC). REC Ref: 22/SS/0106/ IRAS Ref: 317589
I am writing to inform you that your patient named above has consented to participate in the above-named study, sponsored by Imperial College London.
Imperial College London has developed a Decision Support System (DSS) which is a web app available online intended for clinicians to estimate the clinical benefit and risk over time of Lipid Lowering Treatment regimens, whether single or combination therapies. Your patient has been invited to join as they are an adult (up to 80 years of age) with ACS who has recently been hospitalised (within 72 hours).
The aim of this study is to assess whether the availability of the DSS compared to routine care alone results in an increased initiation or intensification of combination LLTs over a 16-week period after an ACS event. This is a cluster randomised trial with a total of 48 hospital sites across the UK, Spain and Italy– 24 DSS sites and 24 non DSS sites. DSS sites will receive a standardised period of training; following the DSS use it is still up to the clinician to choose & prescribe a suitable therapy for the patient.
The participant will be followed up after the study Baseline Visit (i.e. post-ACS event) over a 4 month period as per routine care and study data will be captured accordingly. Aside from participant consent, there are no other participant study procedures.
This study has been approved by the relevant Ethics Committees and Regulatory authorities and will be conducted in accordance with Good Clinical Practice and appropriate regulatory requirements.
Please find enclosed a participant information sheet which provides more details about the study and what it involves for your patient. If you would like further information about the study, please do not hesitate to contact me.
Thank you in advance for your co-operation.

Kind Regards,

XXX

Figure 2. Detailed Workflow for Estimation of the Impact of Lipid-Lowering Therapy Intensification via Monte-Carlo Simulation Based Approach

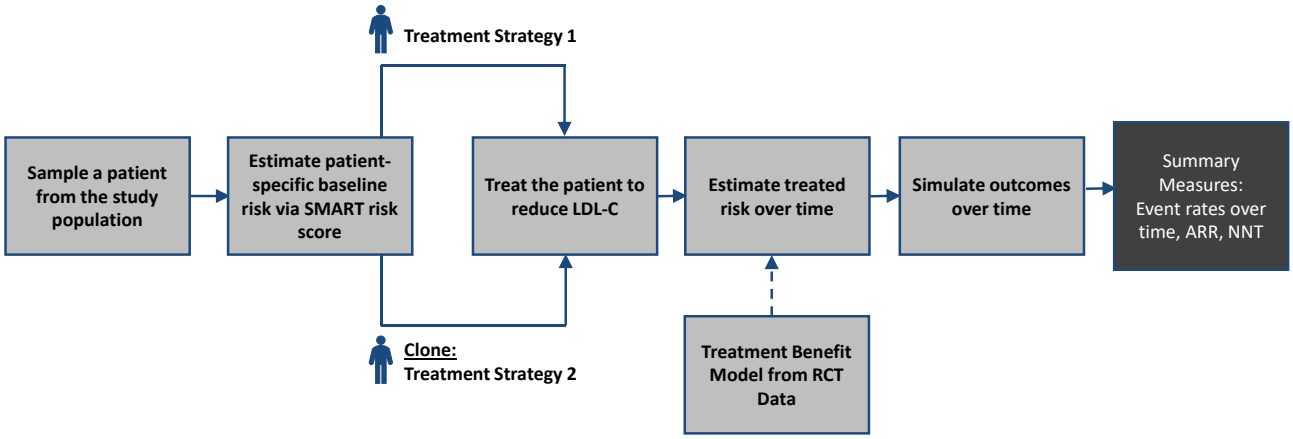

Table 1. Illustration for Reporting Results of Simulation: Estimated Utilization of Lipid-Lowering Therapy

		A: Baseline (Observed SOC in the Database)	**B:** HIS Only at Index ACS	**C1:** HIS at Index ACS + Goal-Based Intensification*	**C2:** HIS + EZE at Index ACS	**C4:** HIS + EZE + PCSK9i at Index ACS
1	MIS Only			NA	NA	NA
2	HIS Only					
3	MIS + EZE			NA	NA	NA
4	HIS + EZE					
5	MIS + PCSK9i			NA	NA	NA
6	HIS + PCSK9i			NA	NA	NA
7	MIS + EZE + PCSK9i			NA	NA	NA
8	HIS + EZE + PCSK9i				NA	
9	EZE Only			NA	NA	NA
10	PCSK9i Only			NA	NA	NA
11	EZE + PCSK9i			NA	NA	NA
12	No LLT			NA	NA	NA

Note: For all scenarios (with the exception of baseline and HIS only at Index ACS) HIS only will be utilized as the comparator strategy. Thus, “NA” has been listed as all patients will be on a minimum of HIS only during follow-up. Further, the sequential application of treatments ensures that patients cannot be treated with ezetimibe without already being treated with HIS, or PCSK9i without already being treated with both HIS and ezetimibe.

* Ezetimibe added at 6 months and PCSK9i added at 12 months depending on LDL-C goal achievement (both LDL-C <1.4 mmol/L (55 mg/dL) and ≥50% reduction in LDL-C)

Table 2. Illustration for Reporting Results of Simulation: Estimated LDL-C Goal Achievement

	A: Baseline (Observed SOC in the Database)	**B:** HIS Only at Index ACS	**C1:** HIS at Index ACS + Goal-Based Intensification*	**C2:** HIS + EZE at Index ACS	**C3:** HIS + EZE + PCSK9i at Index ACS
At 0-months					
LDL-C < 55 mg/dL					
55 ≤ LDL-C < 70 mg/dL					
70 ≤ LDL-C					
At 6-months					
LDL-C < 55 mg/dL					
55 ≤ LDL-C < 70 mg/dL					
70 ≤ LDL-C					
At 12-months					
LDL-C < 55 mg/dL					
55 ≤ LDL-C < 70 mg/dL					
70 ≤ LDL-C					

* Ezetimibe added at 6 months and PCSK9i added at 12 months depending on LDL-C goal achievement (both LDL-C <1.4 mmol/L (55 mg/dL) and ≥50% reduction in LDL-C)

Table 3. Illustration for Reporting Results of Simulation: Estimated LDL-C Goal Achievement

	A: Baseline (Observed SOC in the Database)	**B:** HIS Only at Index ACS	**C1:** HIS at Index ACS + Goal-Based Intensification*	**C2:** HIS + EZE at Index ACS	**C3:** HIS + EZE + PCSK9i at Index ACS
At 0-months					
LDL-C < 55 mg/dL + LDL-C Reduction ≥ 50%					
LDL-C < 55 mg/dL + LDL-C Reduction < 50%					
LDL-C ≥ 55 mg/dL + LDL-C Reduction ≥ 50%					
LDL-C ≥ 55 mg/dL + LDL-C Reduction < 50%					
At 6-months					
LDL-C < 55 mg/dL + LDL-C Reduction ≥ 50%					
LDL-C < 55 mg/dL + LDL-C Reduction < 50%					
LDL-C ≥ 55 mg/dL + LDL-C Reduction ≥ 50%					
LDL-C ≥ 55 mg/dL + LDL-C Reduction < 50%					
At 12-months					
LDL-C < 55 mg/dL + LDL-C Reduction ≥ 50%					
LDL-C < 55 mg/dL + LDL-C Reduction < 50%					
LDL-C ≥ 55 mg/dL + LDL-C Reduction ≥ 50%					
LDL-C ≥ 55 mg/dL + LDL-C Reduction < 50%					