Implementation of an Evidence-Based Home Cardiac Rehabilitation Programme for People with Heart Failure & Their Caregivers in Scotland

SCOT: REACH-HF (ISRCTN53784122)

STATISTICAL ANALYSIS PLAN (SAP) v1.0_16th January 2021

Prepared by Professor Prof Rod Taylor. MSc, PhD
Professor of Population Health Research
MRC/CSO Social and Public Health Sciences Unit & Robertson Centre for Biostatistics, Institute of Health and Well Being, University of Glasgow

AMENDMENT HISTORY

Amend no.	Protocol version no.	Date	Author	Details of changes made
				•
				•

RESEARCH REFERENCE NUMBERS

IRAS number:	276172
ISRCTN number / Clinical trials.gov number:	ISRCTN53784122
SPONSOR'S number:	GN20CA013
FUNDER'S number:	RG2685/19/21

1. INTRODUCTION

1.1. Background

This plan is based on the SCOT:REACH-HF protocol version 2.1 4th May 2021 and published version [1. See trial protocol for details of study objectives, design, sample size, study population, and study outcomes.

1.2 SAP objective

The objective of this statistical analysis plan (SAP) is to describe the statistical analyses to be carried out for the SCOT:REACH-HF Study based on the quantitative patient and caregiver outcomes. The SAP is drafted in accordance with the Glasgow Clinical Trials Unit guideline 10.003A 'Statistical Analysis Plans for Clinical Trials', JAMA guidelines for statistical analysis plans [2] , the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting recommendations [3], and Standards for Reporting Implementation Studies (StaRI) Statement [4].

2. ANALYSIS POPULATIONS

2.1. Efficacy and safety

All statistical analyses will be based on the population of patients and caregivers who consented to participation.

3. ANALYSIS

3.1. Subject disposition

We will summarise the patient and caregiver screening, recruitment, level of intervention participation, and baseline and follow up outcome completion using a flow diagram (see dummy Figure 1).

3.2. Baseline characteristics

The demographics, medical history, concomitant medications of patients at baseline and demographics of caregivers will presented descriptively using means (and standard deviations) and frequency (%s) for continuous and categorical outcomes respectively and number of participants (see dummy Tables 1a & 1b).

3.3. Efficacy outcomes

3.3.1. Primary & secondary outcomes

The patient and caregiver reported outcomes are summarised in the table below together with reporting metrics and outcome ranges. Additional patient efficacy

outcomes included: exercise capacity based incremental shuttle walk test (although with COVID-19 it was only possible to collect this outcome in a very small number of patients) and hospitalisations (all cause and heart failure – number and duration).

3.3.2. Other outcomes

Facilitator data: (1) facilitators are asked to complete a facilitator resource log (1 per participant) summarising number of contacts (intervention sessions) with each patient (including whether in person/by phone), and any adaptations made; (2) facilitators are asked to complete a brief self-rated fidelity checklist after each session they deliver. This comprises questions about the same 12 main intervention components and allows the facilitators to rate the occurrences of each feature (absence, minimal, some, sufficient, good, very good, excellent). This data will be presented descriptively.

3.3.3. *Methods of statistical analysis*

All patient and caregiver outcomes will be summarised using descriptive statistics (means & standard deviations) at baseline and 4-month follow up (see dummy table 2). The primary analysis will be a within participant comparison of all outcomes baseline versus four months follow up. All within-patient outcome comparisons will be presented as mean difference with 95% CI (see dummy table 2).

All statistical analysis will be conducted using STATA v.17.0 or later.

3.3.4. *Sub-group analyses*

Given relatively small nature of the study, no sub-group analyses will be undertaken.

3.3.5. *Handling missing outcome data*

We will examine the characteristics of any patients who drop out. Given the implementation nature of the study no imputation of their missing outcome data will be undertaken.

3.4. Safety outcomes

We collected serious adverse events (SAEs) i.e., death or events that resulted in hospitalisations. SAEs will be reported descriptively (see dummy table 3).

	Scoring summaries	Score range	Score interpretation	Minimal important difference
Patient-reported outcomes				
Primary outcome				
Minnesota Living with Heart Failure Questionnaire (MLHFQ)	Total score Physical component score (PCS) Mental component score (MCS)	0 to 155 0 to 80 0 to 80	Lower the score the higher the HRQoL	5 points [5]
Secondary outcomes				
EuroQol (EQ-5D-5L)	Overall VAS score Total utility score	0 to 100 0.00 to 1.00	Higher the score the better the HRQoL	0.2 [6]
Self-Care of Heart Failure Index (SCHFI)	Self-care maintenance Symptom perception Self-care management	0 to 100 (standardised)	Higher score indicating better self-care.	None identified [7]
Health Literacy Questionnaire (HLQ)	Feeling understood and supported by healthcare providers (HPS) Having sufficient information to manage my health (HSI)	1 to 4 1 to 4 1 to 4	Higher the score higher the HL	*

	Actively managing my health (AMH) Social support for health (SS) Appraisal of health information (CA) Ability to actively engage with healthcare providers (AE) Navigating the healthcare system (NHS) Ability to find good health information (FHI)	 1 to 4 1 to 4 1 to 5 1 to 5 1 to 5		
Hospital Anxiety and Depression Scale (HADS)	HADS-A HADS-D	0 to 21 0 to 21	Higher the score the higher depression/anxiety	Score of >8 denotes clinical cut-off MCID 1.7 points[8]
PROM-CR	Overall Health & Well-being Total Physical Impact Overall Physical Well-being Total Social Impact Overall Social Well-being Overall Emotional Well-being	0 to 10 0 to 40 0 to 10 0 to 30 0 to 10 0 to 10	Higher better Lower better Higher better Lower better Higher better Higher better	*

	Impact of Care	0 to 25	Higher better	
Resource use and costs?	See health economic sections of this document	Not applicable	Not applicable	
Caregiver outcomes				
EuroQol (EQ-5D-5L)	Overall VAS score Total utility score	0 to 100 0.00 to 1.00	Higher the score the better the HRQoL	0.2 [6]
Hospital Anxiety and Depression Scale (HADS)	HADS-A HADS-D	0 to 21 0 to 21	Higher the score the higher depression/anxiety	Score of >8 denotes clinical cut-off MCID 1.7 points [7]
Family Caregiver Quality of Life Scale questionnaire (FamQol)	Physical subscale Psychological subscale Social subscale Spiritual subscale General QoL	4 to 20 4 to 20 4 to 20 4 to 20 16 to 80	Higher the score the better the HRQoL	*
Caregiver Burden Questionnaire HF (CBQ-HF)	Emotional Social life Lifestyle	0 to 60 0 to 8 0 to 8	Higher the score the higher the burden	*

Caregiver Contribution to Self-care of HF Index questionnaire (CC-SCHFI)	Maintenance Management maintenance Confidence maintenance	0 to 100 0 to 100 0 to 100	Higher scores indicating higher contribution to self-care	*

*no minimum important difference could be located

3.6. Health economic analyses

The economic analysis will focus on the cost of the delivery of REACH-HF in the four sites. The additional (incremental) costs associated with delivery of the Heart Failure Manual, when added to usual care, will be estimated using resource use data collected within-trial. Resource use is expected to consist of time input from REACH-HF facilitators, supervision for facilitators, training costs for facilitators, and consumables (e.g. Heart Failure Manual packs). Data on facilitator time input will be captured via facilitator self-report (Facilitator Logs) within trial at participant level. Unit costs for resource use will be sought from national published or NHS sources (see dummy table 4).

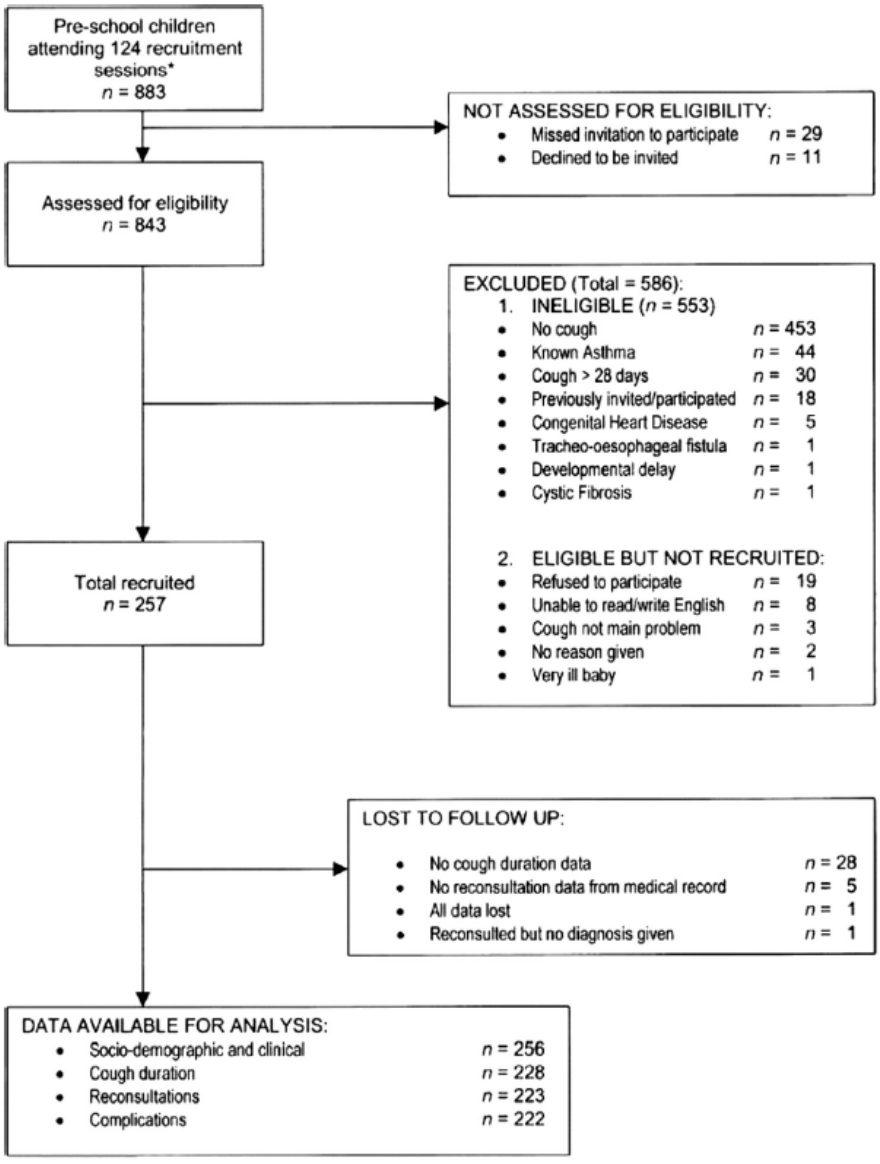
Data collected:
Resource use: primary care; secondary care; social care; support from others.
From resource log: facilitators time outside intervention sessions, mileage etc (sundry costs)
Cost of REACH-HF facilitator training: a) information to be provided by Heart Manual office, along with request for specific staff time costs (by band/grade); or b) use a standard cost per training participant (facilitator).

3.7 References

1. Purcell C, Daw P, Kerr C, Cleland J, Cowie A, Dalal HM, Ibbotson T, Murphy C, Taylor R. Protocol for an implementation study of an evidence-based home cardiac rehabilitation programme for people with heart failure and their caregivers in Scotland (SCOT:REACH-HF). *BMJ Open.* 2020;10:e040771.
2. Gamble C, Krishan A, Stocken D, Lewis S, Juszczak E, Doré C, Williamson PR, Altman DG, Montgomery A, Lim P, Berlin J, Senn S, Day S, Barbachano Y, Loder E. Guidelines for the Content of Statistical Analysis Plans in Clinical Trials. JAMA. 2017;318:2337-2343.
3. Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, Poole C, Schlesselman JJ, Egger M; STROBE Initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *Int J Surg.* 2014;2:1500-24.
4. Pinnock H, Barwick M, Carpenter C R, Eldridge S, Grandes G, Griffiths C J et al. Standards for Reporting Implementation Studies (StaRI) Statement *BMJ.* 2017; 356 :i6795
5. American Thoracic Society. *Minnesota Living with Heart Failure Questionnaire*. 2004. New York: American Thoracic Society; 2004. http://qol.thoracic.org/sections/instruments/ko/pages/MLWHFq.html
6. Feng YS, Kohlmann T, Janssen MF, Buchholz I. Psychometric properties of the EQ-5D-5L: a systematic review of the literature. *Qual Life Res.* 2021;30:647-673.
7. Vellone E, De Maria M, Iovino P, Barbaranelli C, Zeffiro V, Pucciarelli G, Durante A, Alvaro R, Riegel B. The Self-Care of Heart Failure Index version 7.2: Further psychometric testing. *Res Nurs Health.* 2020;43:640-650.
8. Lemay KR, Tulloch HE, Pipe AL, Reed JL. Establishing the Minimal Clinically Important Difference for the Hospital Anxiety and Depression Scale in Patients With Cardiovascular Disease. *J Cardiopulm Rehabil Prev.* 201939(6):E6-E11.

DUMMY FIGURES & TABLES

Figure 1. Participant disposition



*Denominator data missing from one session at which at least 3 attended with cough, 2 recruited

Table 1a. Baseline characteristics of included patients

	N = x patients
Demographics	
Age – years, mean (SD)	
Gender– male, n, (%)	
Height (m)	
Weight (kg)	
Ethnicity White Black Caribbean Black African Black other Chinese Bangladeshi other	
Partnership status Single Divorced Married or civil partnership Widowed Prefer not to say	
Who living with Live alone Children < 18 yrs Children > 18 yrs No-family Spouse-partner Parent Other family Prefer not to say	
Smoking status Never smoked Used to smoke Currently smoke Prefer not to say	
Employment status	

In employment or self-employment Student Unemployed Full parent/carer Prefer not to say	
Continue education after school leaving	
Degree or equivalent education	
Medical history	
Ejection fraction - %, mean (SD)	
Cause of HF? (non/ischaemic)	
NYHA - n, (%) Class I Class II Class III Class IV	
Angina pectoris	
Arthritis (osteo or rheumatoid)	
Asthma	
Atrial fibrillation or atrial flutter	
Cardiac arrest with resuscitation	
Cerebrovascular disease	
Chronic back pain	
Chronic renal impairment	
Depression	
Hypertension	
Myocardial infarction	
Osteoporosis	
Stroke	
Valvular heart disease	
Treatments	
CAGB	
Coronary angioplasty (with or without stent)	
Implantable cardioverter defibrillator (ICD)	
Cardiac synchronisation therapy device (CRT)	
Combined CRT/ICD device	
Heart transplant	

Pacemaker	
Concomitant medication	
A2 receptor antagonist, n, (%)	
ACE inhibitor	
Aldosterone receptor antagonist	
Anti-coagulant	
Beta blocker	
Digoxin	
Ivabradine	
Loop diuretic	
Nitrate	
Thiazide diuretic	

Table 1b. Baseline characteristics of included caregivers

	N = x caregivers
Demographics	
Age – years, mean (SD)	
Gender – male, n, (%)	
Height (m)	
Weight (kg)	
Ethnicity White Black Caribbean Black African Black other Chinese Bangladeshi other	
Partnership status Single Divorced Married or civil partnership Widowed Prefer not to say	
Who live with Live alone	

Children < 18 yrs Children > 18 yrs No-family Spouse-partner Parent Other family Prefer not to say	
Smoking status Never smoked Used to smoke Currently smoke Prefer not to say	
Employment status In employment or self-employment Student Unemployed Full parent/carer Prefer not to say	
Continue education after school leaving	
Degree or equivalent education	

Table 2. Patient and caregiver baseline versus 4-month outcome scores

	Baseline **N, Mean (SD)***	**4-months** **N, Mean (SD)***	**Baseline-4-month difference** **Mean (95% CI), P-value**
Patient-reported outcomes			
Primary outcome			
MLHFQ Total score PCS MCS			
Secondary outcomes			
EQ-5D-5L Overall VAS score Utility score			
HLQ HPS HSI AMH SS CA AE NHS			

FHI			
HADS-A HADS-D			
PROM-CR			
ISWT, meters			
Caregiver outcomes			
EQ-5D-5L Overall VAS score Utility score			
Hospital Anxiety and Depression Scale (HADS)			
Family Caregiver Quality of Life Scale questionnaire (FamQol)			
Caregiver Burden Questionnaire HF (CBQ-HF)			
Caregiver Contribution to Self-care of HF Index questionnaire (CC-SCHFI)			

*consider median (upper /lower quartile) if data non-normal

Table 3. Patient serious adverse events

	Number of patients	Number of events	Reasons
Hospitalisation	n/N (%)	n	
etc			

Table 4. Costs of REACH-HF (taken from RCT paper)

Table S2. REACH-HF intervention contacts and costs (n=94)

Contacts/item	Contacts (n)	Duration (mins)	
		Contact	Non-contact (planning)
Contacts			
Face-to-face contacts	3.96 (1.2) [2, 7]	69.15 (28.4) [8, 170]	35.96 (34.1) [5, 200]
Telephone contacts	2.51 (2.37) [0, 9]	18.89 (9.06) [2, 50]	13.68 (12.8) [0, 100]
Total contacts	6.52 (2.63) [3, 13]		
Total time			
Face-to-face contacts		271.45 (93.6)	
Telephone contacts		47.41 (49.6)	
Total planning and non-contact time			
Face-to-face		141.91 (89.9)	
Telephone		34.35 (42.2)	
Overall total time input (excluding travel time, as allowance already in unit cost estimate)		495.13 (180) [175, 1190]	
Costs (£/$)			
Cost per hour* (33)		44.00/61.97	
Estimated total delivery cost (HF facilitator)*		362.93/509.90 (131.96/185.86)	
Other resource use and costs†			
Consumables (1 REACH-HF Manual)		25.00/35.21	
DVDs (2 at £7.50/$10.56 each)		15.00/21.13	
Distribution of HF facilitator training costs, per participant†		15.47/21.79	
Estimated total delivery cost for REACH-HF Manual‡		418.39/589.28 (207.14/291.75 to 733.28/1,032.79)	

CI = confidence interval; HF = heart failure; REACH-HF = Rehabilitation EnAblement in CHronic Heart Failure; SD = standard deviation.
*Staff unit costs: grade equivalent to 'community nurse', based on United Kingdom's Agenda for Change band 6, estimated cost per hour (33), includes salary, salary on-costs, overheads (management costs and non-staff costs (including travel and transport)) and capital overheads and excludes costs for qualifications.
†Other cost components: training cost per REACH-HF facilitator specific to delivery of the REACH-HF intervention are estimated at £1547 (see web appendix for further detail), these costs are distributed across the first 100 participants and patients receiving the intervention at £15.47 per participant.
‡When simulating uncertainty in the major cost component of time input for HF facilitator (mean time 495.13 (SD 180) mins) and holding other costs constant (£58.97 per patient) over 1000 simulations provides an estimated overall cost per patient or participant of £438.57 (median £413.57, 95% CI £207.14 to £733.28).