Plan for statistical analyses
The DANREHAB Trial
Primary and secondary outcomes

November 2004
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Based on the scientific protocol of the DANREHAB Trial, the plan for statistical analysis of primary and secondary outcome measurements are described in this document.

The statistical analyses will be carried out blinded by the study independent statistician Søren Rasmussen, National Institute of Public Health who will follow this plan step by step when analyzing the data.

This paper has been approved by signature by the Scientific committee, the principal investigator, and the statistician in charge of the analyses.

November 04

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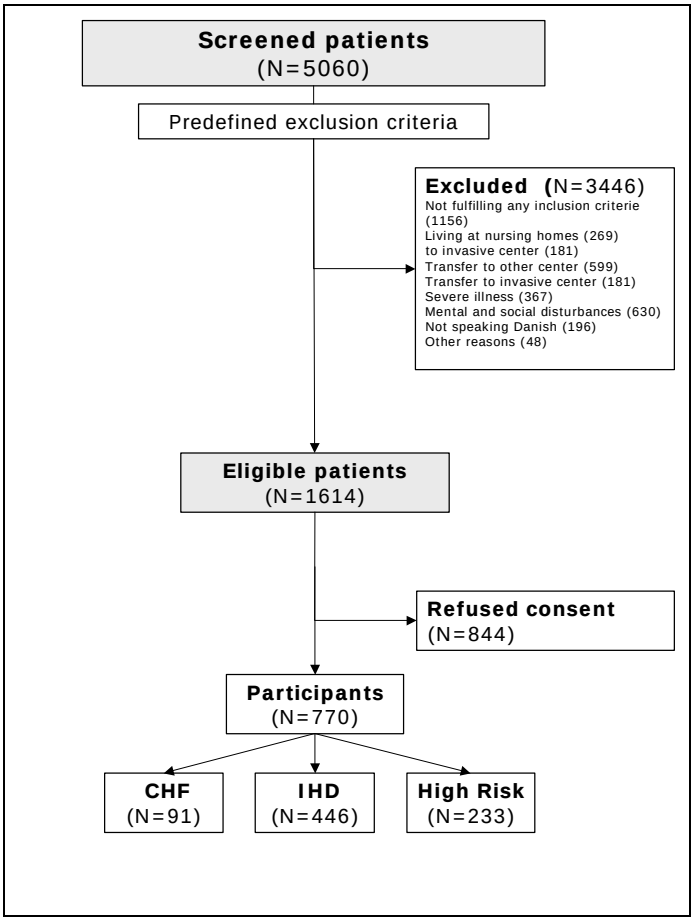
Chair of Steering Committee	Principal investigator	Study-independent statistician

1. About the trial

Current guidelines broadly recommend comprehensive cardiac rehabilitation (CR), although evidence for this is still limited. It is not known whether evidence from before 1995 is still valid.

The DANREHAB Trial was designed as a centrally randomized clinical trial to clarify whether hospital-based comprehensive CR is superior to usual care (UC) for patients with congestive heart failure, ischemic heart disease, or high risk for ischemic heart disease. The CR was an individually tailored, multidisciplinary program (6 weeks of intensive CR and 12 months of follow-up) including patient education, exercise training, dietary counseling, smoking cessation, psychosocial support, risk factor management, and clinical assessment.

Figure 1. Flow of patients through the DANREHAB Trial



The trial design and material are further described in a separate paper[1].

2. Definitions

In the following the outcome variables and level of analysis are defined.

Primary outcome

A combined primary outcome measure including total mortality, myocardial infarction or acute readmissions due to heart disease which ever came first as defined below.

Secondary outcome
a) Total mortality Will be drawn from The National Civil Register, which records the vital status and addresses of all inhabitants in Denmark, when all patients have been followed for at least 12 months from inclusion in study.

b) Myocardial infarction (MI) Will be drawn from The National Patient Registry. It is defined as admissions with the following ICD-10:

I21-I22	primary or secondary diagnosis

c) Readmission due to other heart disease Will be drawn from the National Patient Registry. It is defined as admissions with the following ICD-10:

I10-I50	primary diagnosis	excluding	I26-I28: Pulmonary heart disease I29-I45: Other heart disease (Myo.-, peri.-endocarditis, valvular disease) I21-I22: MI defined above
Z03.4-Z03.5	primary diagnosis		

Intention-to-treat analyses
All randomized patients will be included in the intention-to-treat analysis using the central randomization code delivered from the Copenhagen Trial Unit. The main conclusions of the trial will be drawn on the basis of the intention-to-treat analyses. Patients lost during follow-up will be censored at dropout.

As-treated analyses
Per-protocol analyses will only include the patients who received the planned intervention. As-treated is defined as patients, who have followed a full programme as defined below. The As-treated group will be compared to the usual care group. A sensitivity analyses will be conducted according the three intervention groups defined below under Step 2. These analyses will only be considered as explorative analysis.

3. Blinding of statistician
The statistician will only be introduced to this paper and a paper on trial design. When the study-committee has approved the validated end-point variables and the designs of the tables and figures the randomization code will be uncovered. Scheduled to December 2th, 2004.

4. Stepwise analyses for primary and secondary outcome measure

Step 1: Baseline characteristics and comparison between the two intervention groups

Baseline Information	Type	Cut-off point	Generated from	Variable name
Demographic data				
Age groups	Numeric (years)	<65,65-74,75+	CPRNR	AGE
Sex	0,1		CPRNR	SEX
Living alone	0,1		A1500	A1500
Working	0,1		A1510,A1512,A1522	ERHV
Level of education	3 categories		A1530,A1532,A1534	UDD
History of disease				
Diagnosis groups	3 categories	CHF, IHD, HR	STRGRP	STRGRP
MI	0,1		A0210,A0230	MI
PTCA	0,1		A0320	PTCA
CABG	0,1		A0330	CABG
Diabetes mellitus	0,1		A0810	DM
Hypertension	0,1		A0820	A0820
Hypercholesterolaemia	0,1		A0830	A0830
Severity of illness	Index	Groups: 0,1,2+	Based on LPR-codes*	charlson
Time of IHD diagnosis	0,1		Based on LPR-codes**	primary_contact
Medication				
Aspirin	0,1		ASA_0	ASA_0
Beta-blockers	0,1		BETA_0	BETA_0
Calcium antagonists	0,1		CA_0	CA_0
ACE inhibitors	0,1		ACEI_0	ACEI_0
Nitrates	0,1		NTG_0	NTG_0
Lipid lowering drugs	0,1		STATIN_0	STATIN_0
Lifestyle				
Smoker	3 catagories	1: current 2: former 3: never	A1100,1104	SMOKER
Current Smoking	0,1		SMOKER	C_SMOK
Physical activity	0,1	1,2 vs. 3,4	A1000	INACTIVE
Risk factors				
Blood pressure sys.	Numeric (mmHg)	140 mmHg	A0822, A7172a	BT_S
Blood pressure dia.	Numeric (mmHg)	90 mmHg	A0824, A7172b	BT_D
Total cholesterol	Numeric (mmol/l)	4.5 mmol/l	AB0591	Total
LDL cholesterol	Numeric (mmol/l)	2.5 mmol/l	AB1595L	LDL
HDL cholesterol	Numeric (mmol/l)	1.1 mmol/l	AB0592	HDL
Triglycerid	Numeric (mmol/l)	2.0 mmol/l	AB1595T	TRIG
Weight	Numeric (kg.)		A0842	WEIGHT
BMI	Numeric (kg/m$^{2)}$	27.5 kg/m^2	A0842,A0840	BMI
Waist circumference	Numeric (cm)	□: 0.80 □: 0.94	A0850	WAIST
Waist to hip ratio	Numeric	□: 0.85 □: 0.90	A0848,A0850	WH_ratio
Study				
Study-period	Date	1:03-2000-04-2001 2:05-2001-02-2002 3:03-2002-02-2003	R_DATO1	PERIOD

*Definition specified in separate paper [1].

Step 2: Programme attendance in intervention group (will be analyzed by principal investigator to ensure blindness) for per-protocol analyses.

Based on a systematic review of all registered attendance and patient charts the intervention group are categorized in the following three groups:

a. All sessions (up till two "before visit" cancellations were accepted, within the 6 weeks programme.)
b. ½ or more of the sessions
c. Less than ½ of the sessions

Step 3: 12 month follow up in two groups (register-based and 12-month visit)

Step 4: Primary outcome measure in the two intervention groups on an intension-to-treat basis analyzed as described in section 5.

Step 5: Secondary outcome measure in the two intervention groups on an intention-to-treat basis.

Step 6: Subgroup analysis (RR)
Including variables as listed under step 1. Medication will be left out due to missing data in the study-period 1 and 2 for medication at baseline.

Step 7: Explorative analysis of tertiary register-based outcome variables

a) Total number of admissions due to heart disease
b) Total length of stay due to heart disease
c) Total numbers of admissions
d) Total length of stay

WHEN CODE IS BROKEN:

Step 8: Explorative analysis of tertiary outcome variables collected at 12-month follow-up visit will be studied in following analysis and will include.

a) Life stile changes (physical activity, smoking and dietary changes including weight)
b) Other risk factors (Blood-pressure, lipids)
c) Level of information
d) Patient satisfaction
e) Self reported health
f) Health related quality of life (SF36), anxiety and depression (HAD)
g) Mediciation

5. Statistical tests

The trial conclusion will mainly be drawn from the intention-to-treat analysis on first outcome event in the CR and UC groups. A two x two tables will be used to describe primary outcome in the to groups. Differences between the groups will be analyzed using Pearson's chi-square test. Two-tailed $P < .05$ is considered significant.

Further analysis will be conducted using Cox regression models including time to first event as outcome variable. This analysis will contribute to knowledge on relations between background variables and outcome measures

The Cox regression model will include relevant background variables with forward and backward selection for model selection to ensure robustness of the results. The proportional hazard assumption will be checked in the final model. Significant background variables are selected with $P < .05$ due to a large numbers of variables. When selecting relevant background existing knowledge on causality and intermediary variables will be taken in to account.

Presenting baseline characteristics continuous variables will be reported as medians and interquartile ranges. Groups will be compared using the Mann-Whitney rank-sum test.

Due to the skewed distribution of length of stay and repeated measurements of admissions on patients these register-based tertiary outcomes will be analyzed simultaneously using multivariate random effect modeling with patients as random effects.[2]

References

1. Zwisler ADO, Schou L, Soja AMB et al. A randomized clinical trial of hospital-based, comprehensive cardiac rehabilitation versus usual care for patients with congestive heart failure, ischemic heart disease or high risk of ischemic heart disease (the DANRHEAB Trial) - design, intervention and population. 2004.Provissionally accepted.

2. Tooze JA, Grunwald GK, Jones RH. Analysis of repeated measures data with clumping at zero. Stat Methods Med Res 2002;11:341-55.