

**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.

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

November 04

Jørgen Fischer Hansen  
Chair of Steering Committee

Ann-Dorthe Zwisler  
Principal investigator

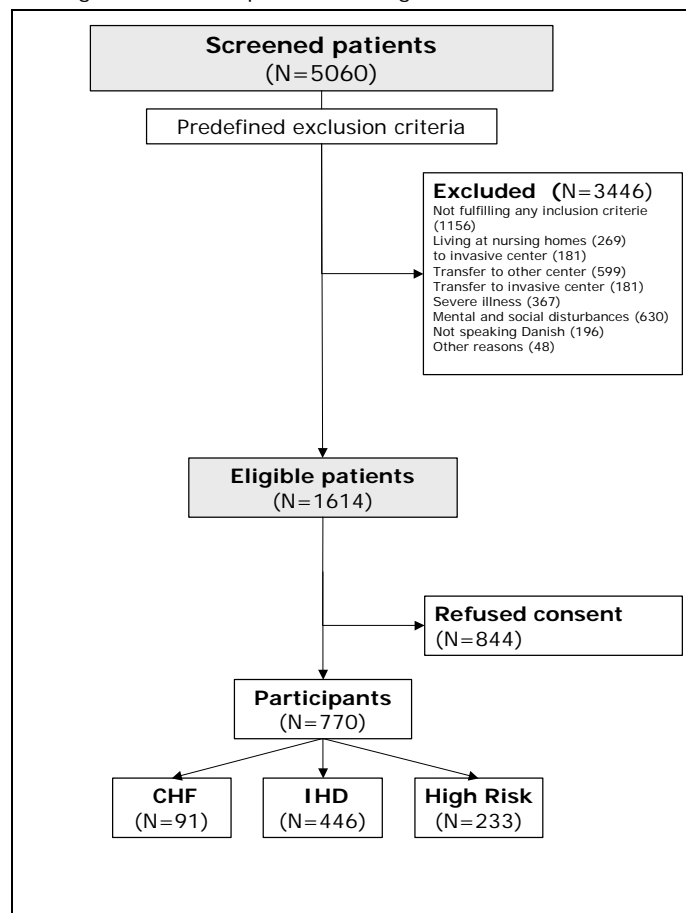
Søren Rasmussen  
Study-independent statistician

## 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<sup>1</sup>.

## 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.



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

**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 intention-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) Medication

## 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.<sup>2</sup>

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## 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. Provisionally 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.