Unique protocol ID: The Swedish DIRECT study

Official title:

Direct letters to relatives at risk of hereditary cancer – a multi-centre randomised controlled trial of healthcare-assisted versus family-mediated risk disclosure at Swedish cancer genetics clinics (DIRECT-study)

Date: 2023-03-27

ClinicalTrials.gov Identifier: NTC04197856

Revised version with full declaration in objectives, related outcome measures and method for statistical analysis.

This version includes clarification in the description of the original outcome measures and also description of the two added secondary objectives (proportion of distant ARRs contacting a cancer genetics clinic).

This attachment also includes clarification of sample size calculation and is presented as an attachment instead of (as previously) in the running text.

As previously, progress criteria and study site audit measures are presented in Table 2.

Objectives, outcome measures and methods for analysis

Research hypothesis

Offering probands direct letters to at-risk relatives (ARRs) as a complement to standard care increases the proportion of ARRs seeking genetic counselling, compared to standard care alone.

Study objectives

Primary objective

- To determine if offering probands direct letters to eligible ARRs as a complement to standard care is superior to standard care alone.
  Outcome measure: The proportion of eligible ARRs contacting a Swedish cancer genetics clinic within 12 months of the proband receiving post-test genetic counselling (all family diagnoses)

Secondary objectives

- To determine if offering probands direct letters to eligible ARRs as a complement to standard care is superior to standard care alone among i) first-degree ARRs and ii) second-degree, third-degree, or more distant ARRs in families with a pathogenic variant in *BRCA1, BRCA2, PALB2, MLH1, MSH2, MSH6 or PMS2*.
  Outcome measure: The proportion of eligible ARR contacting a Swedish cancer genetics clinic within 12 months of the proband receiving post-test counselling because the proband have a pathogenic variant in *BRCA1, BRCA2, PALB2, MLH1, MSH2, MSH6 or PMS2*, among
  - first-degree ARRs and
  - second-degree, third-degree, or more distant ARRs.

- To describe acceptance and distribution of direct letters in the intervention group
  Outcome measure: Proportion of eligible ARRs to whom the probands allowed a letter to be sent, where contact data allowed distribution of letters, and the letters were collected from the post-office within 12 months of the proband receiving the post-test genetic counselling, stratified by study site, gender, and family diagnosis.
  All study outcomes are also presented in Table 1.

Table 1: Outcome measures and methods of statistical analysis for primary and secondary outcomes.

Outcome	**Variable**	**Description**	**Methods of analysis**
Primary	Proportion of ARRs contacting a cancer genetics clinic	Comparing intervention and control group with respect to proportion of ARRs who have contacted a Swedish cancer genetics clinic within 12 months of the proband receiving post-test genetic counselling from the hereditary cancer investigation.	Two-tailed chi-square tests.
	Proportion of ARRs contacting a cancer genetics clinic	Comparing intervention and control group with respect to proportion of ARRs who have contacted a Swedish cancer genetics clinic within 12 months of the proband receiving post-test genetic counselling from the hereditary cancer investigation, taking into account study site, gender, and family diagnosis.	Logistic regression
Secondary	Proportion of first-degree ARRs contacting a cancer genetics clinic	Comparing intervention and control group with respect to proportion of first-degree ARRs who have contacted a Swedish cancer genetics clinic within 12 months of the proband receiving post-test genetic counselling because the proband is a carrier of a pathogenic variant in BRCA1, BRCA2, PALB2, MLH1, MSH2, MSH6, PMS2.	Two-tailed chi-square tests.
	Proportion of distant ARRs contacting a cancer genetics clinic	Comparing intervention and control group with respect to proportion of second-degree, third-degree or more distant ARRs who have contacted a Swedish cancer genetics clinic within 12 months of the proband receiving post-test genetic counselling because the proband is a carrier of a pathogenic variant in BRCA1, BRCA2, PALB2, MLH1, MSH2, MSH6, PMS2.	Two-tailed chi-square tests.
	Acceptance of the intervention	Proportion of ARRs who the probands allowed contact with, stratified by study site, gender, and family diagnosis.	Two-tailed chi-square tests.
	Distribution of direct letters	Proportion of ARRs who the probands allowed contact with and where contact data allowed distribution of the direct letter, stratified by study site, gender, and family diagnosis.	Two-tailed chi-square tests.
	Collection of direct letters	Proportion of ARRs who the probands allowed contact with, where contact data allowed distribution of letters, and the letters were collected from the post-office within 12 months of the proband receiving post-test genetic counselling, stratified by study site, gender, and family diagnosis.	Two-tailed chi-square tests.

Sample size

To detect a difference of 12.5 percentage points in the proportion of listed ARRs between the two study arms (50% vs 62.5%), with a two-sided 5% significance level and a power of 80%, 490 listed ARRs (half in each study group) is required.

At the start of the study period an inclusion target of 600 ARRs was set to ensure well-powered analysis in each subgroup. However, during the study period clinical guidelines in Sweden changed, putting less focus on familial cancer and more on predictive testing leading to a decline in proband influx. To adapt to this change, the initial target of 600 ARRs in total was adjusted to 490 in the most prioritised subgroup, i.e. families with a pathogenic variant identified in a high-risk gene (hereditary breast and ovarian cancer and Lynch syndrome: *BRCA1, BRCA2, PALB2, MSH2, MSH6, MLH1*, *PMS2*).

Table 2. Progress criteria and study site audit measures

	Question	**Pilot outcome**	**Progression criteria**
Clinical uncertainties	Is the direct letter an accepted mode of contact with relatives by participants?	Proportion of previously unnotified relatives that the participant accepts to be contacted by letter	Go: 40-100% Amend: 20-40% Alert: <20%
	Is the psychological reaction to listing details of relatives acceptable during the counselling session?	Any report of severe adverse effects from the listing of relatives among the 20 individuals in the internal pilot.	Go: No reports Amend: 1-2 reports Alert: >2 reports
	How will at-risk relatives react when they pick up a direct letter with information about hereditary cancer risk?	Any report of severe adverse effects from at-risk relatives as response to receiving letter.	Go: No reports Amend: 1-2 reports Alert: >2 reports
Procedural uncertainties	How many eligible patients are invited to join the trial per study site and time?	Number of invited patients per center and month.	Go: >1 patient. Amend: 0-1 patient. (If 0 included the study site may be discontinued.)
	How many eligible patients were invited to join the trial per each study site´s recruitment basis?	Number of invited patients during one month / number of clinical admissions of eligible patients the same month.	Go: >40% Amend: 10-40% Alert: <10%
	Inclusion: How many patients did NOT accept invitation to participate in the study?	Number of patients who decline or do not return their consent form within 4 weeks / number of patients invited.	Go: <30% Amend: 30-50% Alert: >50%
	How many patients return their Consent Forms to the clinics?	Number of Consent forms returned per invited patients 4 weeks before audit.	Go: >40% Amend: 10-40% Alert: <10%
	Is the added time required to administer intervention acceptable in the clinical setting?	Estimated working time per at-risk relative by research nurses and/or trial physicians.	Go: <1 hours Amend: 1min-3h Alert: >3h
	Is it possible to retrieve the data for the final outcome from local patient registries within an acceptable time?	Reported estimated time to fill in the CRF3 per participant.	Go: <2 hour Amend: 2-6 hour Alert: >6 hours
Methodological uncertainties	Does the HCP treat control and intervention group according to study protocol.	Observational data from patient visits reporting deviation from protocol.	Go: No reports Amend: 0-1 reports Alert: >1 reports
	How will the participants in the control arm react when they are NOT offered the service of direct letters to relatives?	Drop-out rates when finding out one has been randomized to the control arm.	Go: 0 drop-outs Amend: 1-2 drop-out Alert: >2 drop-outs