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# Pharmacological treatment for familial amyloid neuropathy (Protocol)

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[Intervention Protocol]

# Pharmacological treatment for familial amyloid neuropathy

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## ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess and compare the efficacy, acceptability, and tolerability of pharmacologic disease-modifying agents for familial amyloid neuropathy (FAP).

## BACKGROUND

### Description of the condition

Familial amyloid polyneuropathies (FAPs) are a group of relentless, disabling and life-threatening hereditary polyneuropathies affecting the somatic and autonomic components of the peripheral nervous system. FAPs are due to endoneurial deposition of amyloid, an insoluble substance constituted from misfolded mutated proteins that aggregate in nonbranching fibrils oriented in a $\beta$-pleated sheet structure. Extracellular deposition of amyloid fibrils usually also occurs in many organs including the heart, kidneys and eyes. Therefore FAPs fall into the category of multisystem diseases (Planté-Bordeneuve 2011). According to the precursor proteins involved in amyloidogenesis, FAPs are classified as follows:

- transthyretin(ATTR)-FAP, also known as FAP type I (Portuguese-Swedish-Japanese type) and type II (Indiana-Swiss or Maryland-German type);
- apolipoprotein AI(AApoAI)-FAP, also known as FAP type III, Van Allen type or Iowa type; and
- gelsolin(AGel)-FAP, also known as FAP type IV, Finnish type or Meretoja type.

FAPs have an autosomal dominant pattern of inheritance. Age at onset, symptomatology, and clinical course of these conditions can be highly variable (Planté-Bordeneuve 2011; Sipe 2014).

#### ATTR-FAP

ATTR-FAP was originally described by Andrade in Portuguese families and then recognised in Sweden, Japan, Ireland and worldwide (Andrade 1952; Rowczenio 2015). Its overall prevalence is


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estimated to be 0.87 to 1.1 per 1,000,000 people (Adams 2014). Transthyretin (TTR) is a plasma transport protein mainly synthesised by the liver. To date, more than 120 amyloidogenic mutations in *TTR* gene have been described; the Val30Met point mutation is the most common cause of ATTR-FAP worldwide (Sekijima 2015). ATTR-FAP typically begins in the fourth decade of life or later, manifesting as a slowly progressive, length-dependent, sensorimotor polyneuropathy, often associated with autonomic involvement. Walking difficulties requiring aid occur after a mean disease duration of six years, with confinement to a wheelchair on average after 10 years of disease (Adams 2014). Neurological manifestations include loss of superficial sensation, such as nociception and thermal sensations, neuropathic pain, and mild to severe autonomic dysfunction, including orthostatic hypotension, sexual impotence, neurogenic bladder, and gastrointestinal dysfunction. Mutated TTR deposition also occurs in other organs; particularly the heart, causing conduction disturbances and restrictive cardiomyopathy, and the eyes, leading to vitreous opacities and gradual visual loss. Renal involvement is uncommon in ATTR-FAP. Studies in Portuguese patients indicate that death occurs within a mean interval of 10.8 years after the onset of symptoms (Hund 2012).

### AApoAI-FAP

AApoAI-FAP was first recognized in Iowa. Apolipoprotein AI (ApoAI) is the major protein constituent of plasma high-density lipoprotein (HDL). ApoAI is synthesised in the liver and small intestine in approximately the same proportions. Sixteen mutations of the *APOAI* gene are associated with AApoAI-FAP (Planté-Bordeneuve 2011). AApoAI-FAP usually begins in the fourth decade of life and is characterised by amyloid deposition in major organs, including the liver, gastrointestinal tract, and kidneys, leading to renal failure. Although a length-dependent polyneuropathy with slow progression can occur in AApoAI amyloidosis, it is not a major feature of the disease.

### AGel-FAP

AGel-FAP was first identified in Finland, but sporadic cases are recognised worldwide. Gelsolin (Gel) is a calcium-dependent actin-binding protein. Two point mutations in the *GEL* gene are known to cause amyloidosis (Planté-Bordeneuve 2011). The first manifestations of AGel amyloidosis occur at age 25 to 30 years and include corneal lattice dystrophy, cranial neuropathies (typically unilateral or bilateral facial paralysis), peripheral sensory neuropathy, and abnormal skin laxity. Cardiac, renal, and pharyngeal abnormalities are less common. The clinical course of AGel-FAP is slow and quite benign, since life-threatening cardiac and renal complications are rare.

AApoAI-FAP and AGel-FAP are very rare conditions, and their worldwide prevalence is unknown.

The diagnosis of FAP is often challenging, especially in the absence of family history and when the clinical presentation is atypical. Amyloidosis is diagnosed by demonstration of amyloid in tissue biopsy specimens, where it appears as Congo red-binding material with characteristic apple-green birefringence under cross-polarised light. DNA testing to identify an amyloidogenic gene mutation is necessary to confirm the diagnosis of FAP (Planté-Bordeneuve 2011).

## Description of the intervention

The treatment of FAPs requires a multidisciplinary approach, including:

- disease-modifying treatments for stopping or slowing down the progression of amyloidogenesis;
- pharmacological agents to manage the symptoms of peripheral and autonomic neuropathy (e.g. neuropathic pain, orthostatic hypotension, bladder and gastrointestinal disturbances); and
- treatment of complications due to severe organ involvement by amyloidosis (i.e. effects on the heart, eye, or kidney).

Overall *TTR* gene mutations account for the majority of FAP cases, thus trials to date have focused on ATTR-FAP. Liver transplantation is the current first-line disease-modifying treatment for selected patients with ATTR-FAP. Since TTR is synthesised mainly in the liver, transplantation suppresses the main source of mutant TTR. Liver transplantation surgery has shown a favourable effect on the progression of peripheral neuropathy in Val30Met ATTR-FAP even in the long term, but autonomic dysfunction is unchanged after liver transplantation, and cardiac, renal and ocular manifestations of the disease are influenced to a lesser degree or not at all. Patients with severe renal or heart failure may benefit from a combined kidney-liver or heart-liver transplant (Adams 2013). However, large numbers of patients are not suitable transplant candidates and would benefit from medical treatment.

Several pharmacological strategies have been used in FAP during the past decades to develop alternatives to transplantation; this is an active field of research with a number of ongoing trials and completed but unpublished studies (Dubrey 2015). Our review will focus on disease-modifying pharmacological agents for FAP, which are the only treatment options for the majority of the FAP population. We do not consider here symptomatic agents for neuropathic pain, orthostatic hypotension, or bladder or gastrointestinal disturbances, as these are covered in other reviews (Chiang 2015; Kempler 2011; Maule 2007). Also, we do not discuss treatments for complications of severe organ involvement.

## How the intervention might work


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Pharmacologic disease-modifying strategies for ATTR-FAP (some of which are approved and some still under investigation) may involve a number of classes of drugs:

- amyloid kinetic stabilisers, such as tafamidis and diflunisal, which bind mutant misfolded TTR, preventing its aggregation in amyloid fibrils;
- amyloid matrix solvents, such as doxycycline and taurodesoxycholic acid, which act to disrupt deposited amyloid fibrils; and
- amyloid precursor inhibitors (i.e. gene therapy with antisense oligonucleotides (ASOs) and small interfering RNA (siRNA)), which block expression of both mutant and wild type TTR reducing amyloid precursor protein synthesis.

In future, patients with ATTR-FAP might benefit from immunisation against amyloid precursors (Dubrey 2015).
To our knowledge, no specific disease-modifying agent for AApoAI-FAP or AGel-FAP is currently available.

### Why it is important to do this review

The purpose of this review is firstly to evaluate the current level of evidence for pharmacologic disease-modifying treatment of FAP, secondly to compare the efficacy of different disease-modifying treatments for FAP, and thirdly to highlight gaps in knowledge that require further investigation.
The review will be of use to people with FAP, healthcare professionals and researchers. It is likely to draw attention to, and be a stimulus for, more research.

## OBJECTIVES

To assess and compare the efficacy, acceptability, and tolerability of pharmacologic disease-modifying agents for familial amyloid neuropathy (FAP).

## METHODS

### Criteria for considering studies for this review

#### Types of studies

As recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), we will include all randomised controlled trials (RCTs) or quasi-RCTs of pharmacological disease-modifying agents for FAPs, compared to placebo or to other disease-modifying agents. If there are too few RCTs and quasi-RCTs to allow us to draw adequate conclusions, we will describe the results of non-randomised studies, such as cohort studies, case-control studies or case reports, in the 'Discussion' section only. We will include studies reported as full-text, those published as abstract only, and unpublished data. There will be no restrictions as to language.

#### Types of participants

We will include studies of patients aged 18 years or older, of either gender, with a diagnosis of FAP based on clinical or neurophysiological evidence of polyneuropathy, or both, and positive DNA testing for *TTR*, *APOAI* or *GEL* gene mutations, irrespective of biopsy confirmation of amyloid deposits. We will include patients with FAP as the leading cause of their neuropathy. We will exclude patients whose neuropathy is attributable to another cause but not those who have comorbidities that may be associated with a neuropathy, where the presenting neuropathy is FAP related. We will consider results for patients with ATTR-FAP and, if existing, with AApoAI-FAP and AGel-FAP separately.

#### Types of interventions

We will consider trials comparing any disease-modifying pharmacological intervention for FAP in any dose and by any route, compared to placebo, no intervention, or any other active comparator. Any previous or concomitant treatment except for other FAP disease-modifying agents will be allowed.

#### Types of outcome measures

As with many rare diseases, there are no validated outcome measures for FAP. Therefore, measures of disease progression and nerve impairment with demonstrated sensitivity and specificity in other axonal neuropathies (e.g. Charcot-Marie Tooth disease (CMT) or diabetic polyneuropathy) will be included.

##### Primary outcomes

The primary outcome measure will be change in disability due to FAP progression measured by the clinical staging of TTR-FAP (FAP stage) (Coutinho 1980), the Polyneuropathy Disability Score (PDS) (Steen 1983), the Modified Norris Test Score (MNT) (Lacomblez 1989), the Portuguese classification system (PCS) (Sales-Luís 1990), the Kumamoto Score (KS) (Tashima 1999), and the Yamamoto Score (YS) (Yamamoto 2007).

##### Secondary outcomes

Secondary outcome measures will include the following:

1. change in impairment associated with nerve function using the Neuropathy Impairment Score (NIS) (Dyck 1995), the Neuropathy Impairment Score of the lower limbs (NIS-LL) (Bril 1999; Dyck 1997), the Neuropathy Impairment Score of the


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upper limbs (NIS-UL) (Lozeron 2013), the Neuropathy Impairment Score plus 7 nerves test (NIS+7) (Berk 2013), the CMT Neuropathy Score (CMTNS) (Shy 2005), the CMT Neuropathy Score second version (CMTNS2) (Murphy 2011), the Neuropathy disability score revised version (NDS) (Abbott 2002), and the Compound Autonomic Dysfunction Test (CADT) (Denier 2007);

2. change in modified body mass index (mBMI), a measure of wasting and autonomic gastrointestinal function, calculated as the product of the BMI and serum albumin concentration (g/L) (Suhr 1984);

3. change in quality of life (QoL) measured with a validated scale or by a patient-reported questionnaire, including the 36-Item Short-Form Health Survey (SF-36) scale (Ware 1992), the Norfolk Quality of Life-Diabetic Neuropathy Questionnaire (Norfolk QOL-DN) (Vinik 2005), the EuroQoL Quality of Life Scale (EQ-5D) (Rabin 2001), and the Karnofsky Performance Status (KPS) (Yates 1980);

4. change in depression severity measured by a validated scale or by a clinical diagnostic interview, including the Beck Depression Inventory (BDI-II) (Beck 1988) and the Hamilton Rating Scale for Depression (HAM-D) (Hamilton 1960);

5. number of patients who died during the trial.

6. Adverse effects will be analysed as follows:

i) number of patients experiencing at least one adverse event;

ii) mild adverse effects measured by the number of patients experiencing mild adverse events;

iii) number of patients who dropped out due to adverse events during the trial as a proportion of the total number of randomised patients;

iv) severe adverse effects (leading to hospitalisation, disability or death).

All outcomes will be assessed after 12 and 24 months of treatment and at the end of the follow-up period. Characteristics of the scores included as primary and secondary outcome measures are reported in Table 1. In order not to miss any side effects, in the data extraction phase we will collect all side effects data reported in the literature and will discuss ways to summarise them post hoc.

## Search methods for identification of studies

### Electronic searches

The Cochrane Neuromuscular Information Specialist will search the Cochrane Neuromuscular Specialised Register for RCTs or quasi-RCTs using the following search terms: 'familial amyloid neuropath*' or its synonyms 'FAP' or 'familial amyloid polyneuropath*' or 'transthyretin(TTR)-related hereditary amyloidosis' or 'apolipoprotein AI-related hereditary amyloidosis' or 'gelsolin-related hereditary amyloidosis' AND 'tafamidis' or 'tafamidis meglumine' or 'FX1006A' or 'diflunisal' or 'dolobid' or 'dolobis' or 'dolocid' or 'MK647' or 'doxycycline' or 'tauroursodeoxycholic acid' or 'RNA-targeted therap*' or 'RNA interfer*' or 'antisense oligonucleotides', or 'ISIS-TTR$_{Rx}$', or 'ISIS 420915' or 'ALN-TTR01' or 'ALN-TTR02'. The Information Specialist will adapt this strategy to search the Cochrane Central Register of Controlled Trials (CENTRAL) (in the Cochrane Register of Studies Online, CRSO), MEDLINE (from January 1966 to present), and Embase (from 1980 to present). There will be no language restriction. The MEDLINE search strategy can be found in Appendix 1.

### Searching other resources

We will review reference lists of all included studies, non-Cochrane systematic reviews and major textbooks on peripheral neuropathies (written in English) for published reports and citations of unpublished research. We will also conduct a citation search via the Web of Science (included studies only) to identify additional studies. We will contact known experts in the field. Complementary searches will be conducted on the WHO International Clinical Trials Registry Platform (ICTRP), ClinicalTrials.gov, and ClinicalTrialsRegister.eu. We will review pharmaceutical companies' websites - www.pfizer.com, www.merck.com, www.isispharm.com, and www.alnylam.com - to identify ongoing trials and additional published or unpublished data.

## Data collection and analysis

### Selection of studies

Three review authors (FM, GZ, and ST) will independently screen titles and abstracts identified by the electronic searches. The same review authors will obtain the full-text reports of all potentially eligible studies for independent assessment. All review authors (FM, GMF, LS, FioM, TC, GZ, and ST) will decide which studies meet the inclusion criteria. We will resolve disagreement about inclusion criteria by discussion and consensus. We will identify and exclude duplicates and will collate multiple reports of the same study so that each study rather than each report is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and a 'Characteristics of excluded studies' table.

### Data extraction and management

Two review authors (FM and ST) will independently extract data from studies selected for inclusion, using a tailored data collection form. We will use 'Characteristics of included studies' tables to present the essential features of the included studies. Two other review authors (GMF and TC) will check the data extraction. We will resolve disagreements by consensus following discussion


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with the remaining authors (LS, FioM, and GZ). We will obtain missing data from trial authors when possible. We will extract the following study characteristics.

1. Methods: study design, total duration of study, details of any 'run in' period, number of study centres and location, study setting, withdrawals, and date of study.
2. Participants: N, mean age, age range, gender, severity of condition, diagnostic criteria, baseline characteristics, inclusion criteria, and exclusion criteria.
3. Interventions: intervention, comparison, concomitant medications, and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.
5. Notes: funding for trial, notable conflicts of interest of trial authors.

One review author (FM) will transfer data into Review Manager (RevMan 2014). A second review author (ST) will check the outcome data entries. A third review author (GMF) will spot-check study characteristics for accuracy against the trial report. When reports require translation, authors will extract data from the translation provided.

## Assessment of risk of bias in included studies

Two review authors (FM and ST) will independently assess risk of bias for each study using the Cochrane ' Risk of bias' tool, as described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). All review authors (FM, GMF, LS, FioM, TC, GZ, and ST) will resolve disagreements by discussion until we reach consensus. We will assess the 'Risk of bias' according to the following domains.

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other sources of bias.

We will grade studies as having high, low, or unclear risk of bias in each of these domains and will provide justifications for our judgements in the 'Risk of bias' tables, with a quote from the study when appropriate. Where information on risk of bias relates to unpublished data or correspondence with a triallist, we will note this in the 'Risk of bias' table.

### Assesment of bias in conducting the systematic review

We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between protocol and review' section of the systematic review.

## Measures of treatment effect

The primary outcome of stage and secondary outcomes of impairment due to nerve function, mBMI, QoL, depression, and dropouts comprise either ordinal data from measurement scales or continuous data, and we will analyse these as continuous variables (Table 1). We will analyse adverse events and death as dichotomous variables.

### Dichotomous data

We will report dichotomous data as risk ratios (RRs), or risk differences (RDs), with 95% confidence intervals (CIs).

### Continuous data

For continuous data, we will calculate mean differences (MDs) or, for outcomes that are conceptually the same but measured in different ways, standardised mean differences (SMDs) and 95% CIs. If some scales increase with disease severity whilst others decrease, we will multiply the mean values from one set of studies by -1 to ensure that all the scales point in the same direction (Higgins 2011).

### Skewed and non-quantitative data

Skewed data and non-quantitative data will be presented descriptively.

## Unit of analysis issues

The unit of analysis will be the participant, which is typically also the unit of randomisation in the type of trials that we will consider. We will take into account the level at which randomisation occurred. For trials with a cross-over design, only results from the first randomisation period will be considered. Where a trial involves more than two treatment arms, especially two appropriate dose groups of the same drug, the different dose arms will be pooled and considered to be one. In case we identify cluster placebo-controlled randomised trials, we plan to use the intracluster correlation coefficient (ICC), where provided, to adjust for cluster effects.

## Dealing with missing data

We will contact study investigators or sponsors in order to request information about missing data. Where possible, we will analyse all outcome measures using an intention-to-treat analysis (ITT), following the principles 'once randomised always analysed' and 'last observation carried forward'. Where this is not possible, and the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results by a sensitivity analysis.


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### Assessment of heterogeneity

In accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), we will quantify heterogeneity using the $I^2$ statistic. Higgins 2011 recommends overlapping intervals for $I^2$ interpretation as follows:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity; and
- 75% to 100%: considerable heterogeneity.

Heterogeneity classification based on $I^2$ will be looked at in conjunction with a visual inspection of the forest plots. We will also use the $Chi^2$ test and its P value to determine the direction and magnitude of the treatment effects.

### Assessment of reporting biases

We will create and examine funnel plots to explore possible small study biases only if there are more than 10 trials in a single analysis.

### Data synthesis

We will use a random-effects model to calculate treatment effects. We choose the random-effects model as it takes into account differences between studies even when there is no evidence of statistical heterogeneity and gives a more conservative estimate than the fixed-effect model. We note that the random-effects model gives added weight to small studies, which can either increase or decrease the effect size. We will apply a fixed-effect model, on primary outcomes only, to see whether it markedly changes the effect size. If the review includes multiple comparisons that cannot be included in the same analysis, we will report the results for each comparison separately.

#### 'Summary of findings' table

We will summarise the main findings of the review using 'Summary of findings' tables according to methods and recommendations described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will include the following outcomes:

1. change in disability;
2. change in impairment associated with nerve function;
3. change in quality of life; and
4. adverse events.

Two authors (FM and ST) will work independently on 'Summary of findings' assessments. We will use the five GRADEpro GDT considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. We will downgrade the quality of studies from high according to whether these considerations are present to a serious degree. We will use footnotes to aid the reader's understanding of our judgements where necessary.

### Subgroup analysis and investigation of heterogeneity

If a study is of doubtful eligibility for the systematic review, appears to be an outlier, or has missing data that are impossible to retrieve, we will perform analyses with and without inclusion of the trial and will compare these results with each other. We plan to consider the following diagnostic subgroups separately:

1. participants with autonomic involvement and participants without autonomic involvement;
2. participants with neuropathic pain and participants without neuropathic pain;
3. participants with cardiac involvement and participants without cardiac involvement; and
4. participants with renal involvement and participants without renal involvement.

If groups within any of the subgroups are found to be significantly different from one another, we will run metaregression for exploratory analyses of additive or multiplicative influences of the variables in question.

We will use the following outcomes in subgroup analyses:

1. change in disability;
2. death;
3. change in quality of life.

We will use the formal test for subgroup interactions in Review Manager (RevMan 2014).

### Sensitivity analysis

We plan to conduct the following sensitivity analyses. We will examine whether the results change and check for the robustness of the observed findings by:

1. excluding trials at high risk of bias (i.e. trials with inadequate allocation concealment and blinding, with incomplete data reporting and/or with high probability of selective outcome reporting);
2. excluding trials with dropout rates greater than 20%;
3. excluding studies funded by the pharmaceutical company marketing each available pharmacological agent;
4. excluding unpublished studies (if there are any).

### Reaching conclusions

We will base our conclusions only on findings from the quantitative or narrative synthesis of included studies for this review. We will avoid making recommendations for practice. Our implications for research will suggest priorities for future research and outline what the remaining uncertainties are for the topic.

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* *Indicates the major publication for the study*

## ADDITIONAL TABLES

**Table 1. Scores included as outcome measures**

| Instrument name | Abbreviation | Score | Direction of response | References | Data analysed as |
|---|---|---|---|---|---|
| ***Stage of disease based on disability or disability*** | | | | | |
| Clinical staging of ATTR-FAP | FAP stage | 1-3 | Higher scores indicate greater disease severity | Coutinho 1980 | Ordinal |
| Polyneuropathy Disability Score | PDS | 0-5 | Higher scores indicate greater walking disability | Steen 1983 | Ordinal |
| Modified Norris Test Score | MNT | 75-0 | Lower scores indicate greater disability | Lacomblez 1989 | Continuous |
| Portuguese classification system | PCS | 0-6 | Higher scores indicate greater disease severity | Sales-Luís 1990 | Ordinal |
| Kumamoto Score | KS | 0-96 | Higher scores indicate greater disease severity | Tashima 1999 | Continuous |
| Yamamoto Score | YS | 0-4 | Higher scores indicate greater disease severity | Yamamoto 2007 | Ordinal |
| ***Impairment due to nerve function*** | | | | | |
| Neuropathy Impairment Score | NIS | 0-244 | Higher scores indicate greater deficits | Dyck 1995 | Continuous |
| Neuropathy Impairment Score in the lower limbs | NIS-LL | 0-88 | Higher scores indicate greater deficits | Bril 1999; Dyck 1997 | Continuous |


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**Table 1. Scores included as outcome measures** (*Continued*)

| | | | | | |
|---|---|---|---|---|---|
| Neuropathy Impairment Score in the upper limbs | NIS-UL | 0-116 | Higher scores indicate greater deficits | Lozeron 2013 | Continuous |
| Neuropathy Impairment Score plus 7 nerve tests | NIS+7 | 0-270 | Higher scores indicate greater deficits | Berk 2013 | Continuous |
| Charcot-Marie Tooth Neuropathy Score | CMTNS | 0-36 | Higher scores indicate greater deficits | Shy 2005 | Continuous |
| Charcot-Marie Tooth Neuropathy Score 2nd version | CMTNS2 | 0-36 | Higher scores indicate greater deficits | Murphy 2011 | Continuous |
| Neuropathy Disability Score revised version | rNDS | 0-10 | Higher scores indicate greater deficits | Abbott 2002 | Continuous |
| Compound Autonomic Dysfunction Test | CADT | 0-16 | Higher scores indicate greater autonomic impairment | Denier 2007 | Continuous |
| ***Wasting and autonomic gastrointestinal function*** | | | | | |
| Modified body mass index | mBMI | Product of the BMI and serum albumin concentration (g/L) | - | Suhr 1984 | Count |
| ***Quality of life*** | | | | | |
| Short Form 36 Health Survey Questionnaire | SF-36 | 100-0 | Lower scores indicate worse status | Ware 1992 | Continuous |
| Norfolk Quality of Life-Diabetic Neuropathy Questionnaire | Norfolk QoL-DN | 2-138 | Higher scores indicate worse status | Vinik 2005 | Continuous |
| EuroQoL Quality of Life Scale | EQ-5D | 5-15 | Higher scores indicate worse status | Rabin 2001 | Continuous |
| Karnofsky Performance Status | Karnofsky | 100-0 | Lower scores indicate worse status | Yates 1980 | Continuous |


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**Table 1. Scores included as outcome measures** (*Continued*)

| | | | | | |
|---|---|---|---|---|---|
| **Depression** | | | | | |
| Beck Depression Inventory 2nd version | BDI-II | 0-63 | Higher total scores indicate more severe depressive symptoms | Beck 1988 | Continuous |
| Hamilton Depression Rating Scale for Depression | HAM-D | 0-50 | Higher total scores indicate more severe depressive symptoms | Hamilton 1960 | Continuous |

# APPENDICES

## Appendix 1. MEDLINE (OvidSP) search strategy

Database: Ovid MEDLINE
Search Strategy:
---
1 randomized controlled trial.pt. (409862)
2 controlled clinical trial.pt. (90286)
3 randomized.ab. (339499)
4 placebo.ab. (167537)
5 drug therapy.fs. (1829870)
6 randomly.ab. (244645)
7 trial.ab. (351029)
8 groups.ab. (1528474)
9 or/1-8 (3683287)
10 exp animals/ not humans.sh. (4203554)
11 9 not 10 (3168145)
12 Amyloid Neuropathies, Familial/dt (45)
13 Amyloid Neuropathies/dt [Drug Therapy] (24)
14 limit 13 to yr="1994 - 2001" (10)
15 amyloidosis/dt (1118)
16 peripheral nervous system diseases/ (20682)
17 15 and 16 (12)
18 limit 17 to yr="1966 - 1994" (7)
19 or/12,14,18 (62)
20 (familial amyloid adj2 (neuropath$ or polyneuropath$)).mp. (721)
21 (transthyretin adj3 amyloidosis).mp. (501)
22 transthyretin TTR fap.mp. (2)
23 (fap type 1 or fap type I or fap type 2 or fap type II or fap type 3 or fap type III or fap type 4 or fap type IV).mp. (56)
24 apolipoprotein A1-related hereditary amyloidosis.mp. (0)
25 (Apolipoprotein adj5 FAP).mp. (3)


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26 (apolipoprotein adj5 hereditary amyloidosis).mp. (5)
27 gelsolin-related hereditary amyloidosis.mp. (0)
28 ((Van Allen type or Iowa type or Finnish type or Meretoja type) and amyloid).mp. (79)
29 or/20-28 (1242)
30 Prealbumin/ (4249)
31 Meglumine/ (3473)
32 FX1006A.mp. (0)
33 Diflunisal/ (467)
34 Doxycycline/ (8062)
35 Taurochenodeoxycholic Acid/ (550)
36 rna interference/ (37178)
37 exp Oligonucleotides, Antisense/ (14489)
38 exp RNA, Antisense/ (87018)
39 (tafamidis or meglumine or FX1006A or diflunisal or dolobid or dolobis or dolocid or MK647).mp. (8124)
40 (doxycycline or tauroursodeoxycholic acid or TUDCA or RNA-targeted therap* or RNA interfer* or antisense oligonucleotides or ISIS TTR* or ISIS 420915 or ALN-TTR0*).mp. (68409)
41 drug$.tw. (1224455)
42 or/30-41 (1370234)
43 19 or (29 and 42) (690)
44 11 and 43 (115)
45 remove duplicates from 44 (115)

## CONTRIBUTIONS OF AUTHORS

ST is the contact person with the editorial base.

FM and ST worked on the methods section.

FM, GMF and TC drafted the clinical section of the background and will respond to the clinical comments of the referees.

FM and ST will respond to the methodology and statistics comments of the referees.

FM, GMF, TC, GZ and ST contributed to writing the protocol.

FM and ST wrote the final draft of the protocol.

All review authors (FM, GMF, LS, FioM, TC, GZ, and ST) will select studies, extract data,and perform data analysis.

All review authors (FM, GMF, LS, FioM, TC, GZ, and ST) will contribute to writing the review.

FM and ST are the guarantors of the final review.

## DECLARATIONS OF INTEREST

Francesca Magrinelli: none known

Gian Maria Fabrizi: none known

Lucio Santoro: none known

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