Systematic review of mortality in Parkinson's disease
Protocol

Background:
There has been considerable debate about how much mortality is increased in Parkinson's disease (PD). Previous studies have reported a wide range of mortality ratios and there is no published systematic review. Some authors suggest the introduction of levodopa in the 1960s has improved survival in PD.

Aim:
1. To perform a systematic review and meta-analysis of studies of mortality in PD.
2. To assess what factors influence heterogeneity between studies.
3. To assess potential predictors of mortality in PD.

Methods:
Inclusion/exclusion criteria
We will include all studies of mortality in PD (or studies of parkinsonism with a large proportion of patients with PD) with follow-up of at least one year reporting either (i) comparisons with a control population (relative risk [RR], standardised mortality ratios [SMRs] or hazard ratios [HR]); (ii) median survival; (iii) percentage survival at a defined time point; or (iv) median duration of disease at death.

We will exclude studies in which fewer than 75% of included patients have idiopathic PD. We will exclude studies restricted to very specific groups of PD patients in this review (such as only very young patients, only demented patients or only surgically-treated patients). Other cohorts of selected patients, such as male cohorts or those restricted to elderly cohorts will be included in the review, but not the meta-analyses.

Identification of relevant studies
We will perform electronic searches of MEDLINE (1946 to latest update), EMBASE (1947 to latest update) CINAHL (1989 to latest update) and Web of Science (1970 to latest update). We will also try to identify relevant grey literature using online databases (www.scirus.com, www.theses.com and www.opengrey.eu). We will also review reference lists and validate our electronic searches with handsearching of selected journals. The electronic search strategies are as follows, including the numbers of results for each search string on 3/10/12:

MEDLINE:

1	exp Parkinsonian Disorders/	53371
2	parkinson:.tw.	64261
3	1 or 2	73117
4	exp mortality/	255657
5	exp cause of death/	32487
6	exp survival rate/	113379
7	exp prognosis/	966986
8	mortality.tw.	384460
9	survival analysis/	91196
10	SMR.tw.	3196
11	deaths.tw.	102573
12	death rate.tw.	8726
13	prognosis.tw.	197043
14	or/4-13	1529352
15	3 and 14	4839
16	exp animals/ not humans.sh.	3785951
17	15 not 16	4604

EMBASE:

1	exp parkinson disease/	82591
2	exp parkinsonism/	20393
3	extrapyramidal syndrome/	5269
4	parkinson:.tw.	90605
5	or/1-4	119004

6	mortality/	487336
7	mortality.tw.	560236
8	deaths.tw.	148758
9	death rate.tw.	13947
10	standardized mortality ratio/	582
11	SMR.tw.	3960
12	survival/ or disease specific survival/ or life expectancy/ or long term survival/ or overall survival/ or survival rate/ or survival time/	395442
13	prognosis/	426405
14	prognosis.tw.	308177
15	or/6-14	1533329
16	5 and 15	4448
17	exp animal/ not human/	1349994
18	16 not 17	4433

CINAHL:

S1	TX Parkinson*	8709
S2	(MH "Parkinsonian Disorders+")	6567
S3	S1 or S2	8790
S4	(MH "Mortality")	11818
S5	TX mortality	92504
S6	TX survival	47756
S7	TX deaths	14598
S8	TX prognosis	36379
S9	S4 or S5 or S6 or S7 or S8	149605
S10	(S3 and S9)	425

Web of Science:

Topic=(Parkinson*) AND Topic=(Mortality or "deaths")	1373

We will examine whether adding certain terms to our search strategy increases the sensitivity of the search (for example, exp cohort studies/ in MEDLINE, exp cohort analysis/ in EMBASE, cohort.tw., life expectancy.tw or survival.tw.). We will do this by searching with the additional terms included on a restricted time period (one or two years). If additional relevant studies are found, we will run the search with the additional terms over the full time period.

Titles and abstracts will be assessed for relevance. The full text of the articles will be obtained for all relevant studies and where it is unclear from the abstract whether a study should be included. Foreign language studies will be translated if possible.

Data extraction and analysis

We will create a data extraction form which will be piloted on a selection of studies and modified as necessary before being used for the rest of the group. We will describe the methods of the studies and assess quality using a checklist modified from the Newcastle-Ottawa Scale. Meta-analysis will be performed, where possible, of RRs, SMRs, HRs, median time from diagnosis to death and proportion dead at specific time points using the Cochrane Collaboration's Review Manager software or StatsDirect using a random effects model.

We will explore heterogeneity with meta-regression, if sufficient data are available. We will assess several covariates including (i) quality of study, (ii) year (including pre- versus post-levodopa era), (iii) study setting (community-based, specialist clinic- or trial-based), (iv) study type (incident versus prevalent cohort), (v) median age at onset, (vi) gender, (vii), median disease duration at study baseline, (viii) baseline disease severity, (ix) duration of follow-up and (x) geographical location.

We will also assess which variables have been studied for their independent predictive impact in included studies and which of those were found to independently predict mortality.