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Palliative Medicine

Development of an evidence base for palliative care triggers in progressive neurodegenerative conditions: a multi-centre retrospective case record review and principal component analysis

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Keywords:	Triggers, Progressive neurodegenerative conditions, Palliative care
Abstract:	<p>Background: The use of specific triggers has been suggested to help identify patients with progressive neurological disease who would benefit from palliative care.</p> <p>Aim: To develop an evidence base for the use of triggers for patients with progressive neurological disease.</p> <p>Design: A retrospective case note review was undertaken in 12 specialist palliative care units across the UK, extracting the timing, and presence of triggers in the last 2 years of life.</p> <p>Results: 300 records were reviewed: MND/ALS 58%, Parkinson's disease 17% and Parkinson's plus syndromes 12%. There was a high burden of triggers – 16 in the last 2 years of life and 10 in the last 6 months of life. Four factors were found to explain 64% of the total variance:</p> <p>Factor 1 – Deterioration in physical function, dysphagia, significant complex symptoms and pain</p> <p>Factor 2 – Weight loss and respiratory symptoms</p> <p>Factor 3 – Recurrent infections and cognitive decline</p> <p>Factor 4 – Aspiration pneumonia</p> <p>A Cox regression analysis showed a statistically significant association, reducing the hazard of death, between Factor 1 and survival. When all diagnoses were grouped together the total number of triggers at 3 months was associated with survival.</p> <p>Conclusion: This study shows that there are high burden of triggers in the last months and years of life and they may be valuable in predicting deterioration in the last 6 to 12 months of life for people with progressive neurological disease as the number of triggers and the frequency of triggers increases as death approaches.</p>

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Research ethics and governance approvals for research involving human subjects	Have you given full details of ethics/governance/data protection approvals with reference numbers, full name of the committee(s) giving approval and the date of approval? If such approvals are not required have you made it explicit within the paper why they were not required. Are details of consent procedures clear in the paper?	Yes
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Palliative care triggers in progressive neurodegenerative conditions: a multi-centre retrospective case record review and principal component analysis

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Abstract

Background: The use of specific triggers has been suggested to help identify patients with progressive neurological disease who would benefit from palliative care.

Aim: This study aimed to develop an evidence base for the use of triggers for patients with progressive neurological disease.

Design: A retrospective case note review of the timing and presence of triggers in the last 2 years of life was undertaken.

Setting/participants: 12 specialist palliative care units across the UK provided data from 300 patients: mean patient age 70 years, 50% male, diagnoses included Motor Neurone Disease 58%, Parkinson's disease 17% and Parkinson's plus syndromes 12%.

Results: There was a high burden of triggers – 17 in the last 2 years of life and 10 in the last 6 months of life. The most frequent triggers were: deteriorating physical function, complex symptoms and dysphagia. Four factors were found to explain 64% of the total variance:

Factor 1 – Deterioration in physical function, dysphagia, significant complex symptoms and pain

Factor 2 – Weight loss and respiratory symptoms

Factor 3 – Recurrent infections and cognitive decline

Factor 4 – Aspiration pneumonia.

Cox regression analyses found different triggers were associated with survival from diagnosis and referral to palliative care across all participants, and for different neurological conditions..

Conclusions: This study demonstrates that there is a high burden of triggers in the last months and years of life and that these could potentially be reduced to fewer components. Prospective studies assessing which triggers are useful for different conditions are now required.

Key Words

Triggers, palliative care, neurodegenerative disease, survival analysis, Motor Neuron Disease, Parkinson’s Disease

What is already known about the topic?

The use of triggers to identify the end of life phase and need for palliative care involvement for patients with progressive neurological conditions has been advocated in several policy documents.

The triggers suggested are based on expert consensus.

There is a need to build an evidence base to inform and evaluate such policy recommendations.

What this paper adds?

The average number of triggers in the last 2 years of life was 17, with an exponential increase in the last 6 months of life.

1 Four factors explained 64% of the variance in the triggers.

2

3 Different triggers were associated with survival from diagnosis and referral to
4 palliative care across all participants, and for different neurological conditions.

5

6 **Implications for practice, theory or policy?**

7 The high burden of triggers in the last few months of life indicates the need for
8 palliative care involvement for this patient group.

9
10 The correlation between triggers suggests the triggers could be reduced to fewer
11 components.

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13 There is evidence that different triggers may help prognostication over different time
14 frames and for different conditions.

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Introduction

The care of people with neurological disease is complex and is a challenge for patients, families and professionals. There is a perceived need for palliative care for this patient group, in particular those with progressive degenerative neurological conditions (PNCs), such as motor neurone disease (MND), Multiple sclerosis (MS), Huntington’s disease (HD), Parkinson’s disease (PD) and the Parkinson Plus syndromes (PD Plus).

The need for palliative care has been discussed within specific disease guidelines (1,2) and for all neurological patients, and in the recent consensus document from the European Association for Palliative Care (EAPC) and the European Academy of Neurology (EAN) it was stressed that ‘palliative care should be considered early in the disease trajectory, depending on the underlying diagnosis’(3).

Although there is a perceived need, many patients with progressive neurological disease do not receive palliative care, and the access to specialist services is more

1 restricted than for cancer patients (4). It has been suggested that this is due to the
2 variability in the progression and prognosis of patients with neurological disease and
3 the difficulty in recognising deterioration and that a patient is at the end of life (4,5).
4
5 The National End of Life Care (NEoLC) Programme framework for end of life care in
6 long term neurological conditions suggested possible triggers for the identification of
7 the end of life phase (the last 6-12 months) in this patient population. These 'triggers'
8 are characteristics or events which have a significance within the disease progression,
9 are readily recognised and can be easily used clinically. The triggers suggested
10 included swallowing problems, recurring infection, marked decline in functional
11 status, first episode of aspiration pneumonia, cognitive difficulties, weight loss and
12 significant complex symptoms (5). The use of such triggers has also been advocated
13 by the Supportive and Palliative Care Indicators Tool (SPICT) (6) and the Marie
14 Curie Triggers for Palliative Care (7) guidance which have suggested that triggers for
15 palliative care involvement are used by service providers to improve palliative care
16 access for such patients.
17
18 The triggers suggested by the NEoLC programme and other guidance are based on
19 expert consensus and there has been little research in this area. It is essential that a
20 robust evidence base is developed to inform and evaluate new palliative care policy,
21 as was illustrated in the review of the Liverpool Care Pathway (LCP) (8). A small
22 study from one centre evaluated the triggers suggested for PNCs and found four
23 symptom components explained 76.8% of the variance (9). These triggers were rapid

1 physical decline, significant complex symptoms including pain, infection and
2 cognitive impairment, and risk of aspiration. In order to further assess the value of the
3 triggers, this study builds on this initial assessment and involved several centres in the
4 UK.

5
6 The objectives of this study were to explore (i) the frequency of triggers for palliative
7 care involvement in PNC in the last 2 years, and 6 months of life, and therefore to
8 identify which triggers are most burdensome for patients with PNCs; (ii) whether the
9 triggers were correlated and if the number of triggers could be reduced to fewer
10 components; (iii) the relationship between the triggers and trigger components, and
11 survival from diagnosis and referral to palliative care services and (iv) the
12 associations between triggers and survival for different diagnoses.

13
14 **Methods**

15
16 *Study design and setting*

17 A retrospective case-note review was conducted by 12 sites from across England and
18 Wales identified through the Association of Palliative Medicine Neurology Specialist
19 Interest Forum (APM Neuro-SIF). All were specialist palliative care services that
20 provide care at: home, hospice unit, in a day hospice or hospital. Data was extracted
21 between January 2014 and 2015. The study was discussed with Leeds East Health
22 Research Ethics Committee and it was agreed that the study met the criteria for UK
23 ethical regulations for research limited to secondary use of anonymised information

1 previously collected in the course of normal care and did not require review by the
2 research ethics committee.

4 *Participants*

5 Consecutive patients who had a diagnosis of a PNC, were under the care of a
6 specialist palliative care service, and had died between January 2009 and 2014 were
7 eligible for inclusion. The local site identified all participants.

9 *Data sources*

10 Members of the clinical team extracted data from the patients' clinical records,
11 including paper case-notes from hospices, hospitals and community teams, as well as
12 electronic databases. A standardised data collection form and a data collection
13 guideline were used to ensure consistency of data extraction across all centres. All
14 data were anonymised locally.

16 *Variables*

17 Data collected included demographic details (e.g. age, gender, and ethnicity), medical
18 history (diagnosis, date of diagnosis, number of comorbidities, date of palliative care
19 referral). For each trigger, according to documented evidence, the timing (in units of
20 months prior to death) of the first presentation and subsequent deterioration of the
21 trigger over the last two years of life were extracted. In addition to the triggers
22 assessed by Hussain et al (9), respiratory symptoms was also included as a trigger as

1 this was considered by the APM Neuro-SIF as a potential important trigger for
2 palliative care involvement in PNC, and in particular MND.
3
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9 *Analysis*
10
11 Descriptive data is summarised by the mean (standard deviation (SD)) or number (%).
12
13 Principal component analysis (PCA) was used to assess the correlation between the
14
15 triggers and to identify common components and therefore whether the triggers could
16
17 be reduced to fewer components. In this type of analysis the correlation between
18
19 parameters (triggers) is attributed to their common dependence on independent
20
21 entities called ‘factors’. The coefficients that link parameters to factors are called
22
23 ‘factor loadings’; the number of factors is chosen to be as small as possible but large
24
25 enough to account for most of the variation within the data. PCA was conducted using
26
27 data from the last six months as there was evidence that the number of triggers
28
29 increased rapidly after this point and to optimise the number of complete cases. It was
30
31 decided *a-priori* that the number of factors in the varimax rotation would be based on
32
33 the number of eigenvalues >1.0 in the PCA. We adopted one common and
34
35 conventional rule of thumb to consider ‘factor loadings’ of 0.40 or larger to be ‘high’.
36
37 Tests of multicollinearity (Bartlett’s test of sphericity $p<0.05$) and sampling adequacy
38
39 (Kaiser-Meyer-Olkin (KMO)) were undertaken to check the analysis was appropriate.
40
41 The internal consistency and reliability of the factors was assessed using Cronbach’s
42
43 α . The least squares regression approach was used to calculate the factor scores,
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45 which are standardized to a mean of zero. The factor scores may then be used as
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47 variables in subsequent modelling (10).
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2 Univariable and multivariable (adjusted for age, gender, diagnosis and comorbidities)
3 Cox regression analyses were used to assess the association of survival from (i)
4 diagnosis and (ii) referral, and:
5 a. factor scores determined by the PCA,
6 b. individual triggers and the number of triggers at 3, 6 and 12 months.

7
8 The Cox regression analyses for survival from diagnosis were repeated according to
9 whether the participants were diagnosed with MND, PD or PD plus. Assessment of
10 the other diagnoses was not possible as the number of participants with the diagnoses
11 was insufficient. A p-value of <0.05 was considered to indicate statistical significance
12 and all analyses were undertaken on STATA (v14.0)

13 14 **Results**

15
16 In total 300 clinical records were reviewed retrospectively. The mean age was 70
17 years (range 35 to 98), 50% were male and 92% were White. The main diagnoses
18 were MND (58%), PD (17%), PD Plus (12%), MS (9%), and HD (2%). The majority
19 had co-morbidities (76%), with 46% having two or more comorbidities.

20 21 **Frequency of triggers for palliative care involvement in PNC in the last 2 years** 22 **and 6 months of life**

1 The average number of total triggers over the last 2 years of life was 16.7 (SD 12.7)
2 and in the last 6 months 10.0 (SD 7.4). Table 1 demonstrates that the most frequent
3 triggers in both the last 2 years and 6 months of life was deteriorating physical
4 function (2 years: 5.0 (SD 4.0), 6 months: 2.9 (SD 2.5)) followed by significant
5 complex symptoms (2 years: 3.9 (SD 5.2), 6 months: 2.3 (SD 3.1)) and dysphagia (2
6 years: 2.5 (SD 2.3), 6 months: 1.5 (SD 1.5)). The same pattern was seen when trigger
7 frequency was assessed per diagnosis for patients with MND, PD, and PD Plus
8 (Appendix Table 1). However for those with MS significant complex symptoms (3.0
9 (SD 3.5)) were slightly more frequent than deteriorating physical function (2.8 (SD
10 3.1)), and for the seven participants diagnosed with Huntington’s disease cognitive
11 impairment was the second most frequent trigger (2.0 (SD 2.1)).

12
13 In the last 2 years of life just over half of patients had documented evidence of weight
14 loss (56%) and pain (56%), and in the last 6 months the figures were just under half
15 (weight loss 42%; pain 44%). Figure 1 illustrates the trend in the total number of
16 triggers according to months prior to death, this demonstrates an exponential increase
17 in the number of triggers over time, with a rapid increase in the last 6 months of life. .

18
19 **Principal component analysis**

20 Factor analysis yielded four separate factors that explained 64% of the total variance
21 in the data set when the eigenvalue =1 criterion was used. Using data from the last 6
22 months of life, the correlation matrix is shown in Table 2. Bartlett’s test of sphericity
23 ($\chi^2=349$, degree of freedom=36, $p<0.0001$) indicated that the correlation between the

variables were sufficiently large for PCA. The KMO measure of sampling adequacy was 0.68, which can be interpreted as the degree of common variance among the variables, and verified the sampling adequacy of the analysis.

Factor analysis, derived from the factor loadings and the analysis of the triggers in last 6 months of life, identified 4 factors, with the following groupings (Table 3):

- Factor 1. Deterioration in physical function, dysphagia, significant complex symptoms and pain
- Factor 2. Weight loss and respiratory symptoms
- Factor 3. Recurrent infections and cognitive decline
- Factor 4. Aspiration.

Factor 1 explained 22% of the variance, the second factor 16%, third factor 14%, and the fourth 12%. Factors 2-4 only loaded on one or two items, so must be interpreted with caution. Cronbach's α were 0.67 for factor 1, 0.37 for factor 2 and 0.26 for factor 3. If "respiratory symptoms" is excluded as a trigger then there is evidence that weight loss, cognitive impairment and infections cluster on the same component and explained 16% of the total variance (data not shown). Higher factor scores on each factor were associated with a higher number of triggers.

Association between triggers and survival in patients with PNC

1 The mean survival time from diagnosis was 56.5 (SD 6.3) months (95% CI: 43.3,
2 67.8) and the median survival 24 months (interquartile range: 64, 11).. The mean
3 survival from referral to palliative care was 29.1 (SD 6.0) months (95% CI: 17.4,
4 40.9) and the median survival was 10 months (interquartile range: 24, 3))..

5
6 *Survival and factor scores:*

7 In a Cox regression analysis assessing the association between the factor scores and
8 survival from diagnosis, there was no statistically significant association at the 5%
9 significant level. This remained the case following adjustments for age, gender,
10 diagnosis and number of co-morbidities (Table 4). In the Cox regression analysis
11 assessing the association between the factor scores and survival from palliative care
12 referral, factor 1 had a statistically significant association (hazard ratio (HR) 0.9, 95%
13 CI 0.76, 0.99)), this remained the case after adjusting for age, gender, diagnosis and
14 number of co-morbidities (HR 0.86, 95% CI 0.75, 0.99). The hazard ratio indicates
15 that an increase in factor 1 scores (deterioration in physical function, dysphagia,
16 significant complex symptoms and pain) reduces the risk of death, after adjustment
17 for the effects of the other variables in the model.

18
19 *Survival and individual triggers:*

20 In a multivariable Cox regression analysis assessing the association between
21 individual triggers and survival from diagnosis, there was evidence that the number of
22 triggers 3 months prior to death and diagnosis had a statistically significant
23 association with survival from diagnosis (Appendix Table 2). When repeated for

1 survival from referral to palliative care, there was evidence that again the number of
2 triggers 3 months prior to death had a statistically significant association with
3 survival, as well as weight-loss in the last 2 years of life and age. There was evidence
4 that the number of documented episodes of cognitive impairment was also associated
5 with survival, however the 95% CI for this crosses 1. As age, episodes of weight-loss,
6 and number of triggers at 3 months increased, the hazard of death increased
7 (Appendix Table 2).

8 9 **Association between triggers and survival for different diagnoses**

10 11 *Survival and factor scores:*

12 The multivariable Cox regression analyses for survival from diagnosis for the MND,
13 PD and PD Plus groups, found evidence that different factors were associated with
14 survival for the different diagnoses (Table 5). For MND there was insufficient
15 evidence that any of the factors scores were associated with survival when age, gender
16 and comorbidities were taken into account. For PD, there was evidence of a
17 significant association with factor 4 (aspiration), and for PD plus there was evidence
18 of a significant association with factor 1 (deterioration in physical function, dysphagia,
19 significant complex symptoms and pain) and factor 3 (recurrent infections and
20 cognitive decline).

21
22 The multivariable Cox regression analyses for survival from palliative care referral
23 for the MND, PD and PD Plus groups, also found evidence that different factors were

1 associated with survival for the different diagnoses (Table 5). For MND there was
2 insufficient evidence that any of the factors scores were associated with survival when
3 age, gender and comorbidities were taken into account. For PD, there was evidence of
4 a significant association with factor 1 and factor 4, and for PD plus there was
5 evidence of a significant association with factor 2, factor 3 and factor 4.

6
7 *Survival and individual triggers:*

8 The multivariable Cox regression analysis assessing the association between
9 individual triggers and survival from diagnosis, found for MND: being female and the
10 number of triggers at 3 months prior to death increased the hazard of death, for PD:
11 increasing number of aspirations increased the hazard of death, for PD plus: more
12 infections and episodes of cognitive impairment increased the hazard of death,
13 however as the total number of triggers at 6 months increased the hazard of death was
14 found to decrease (Appendix Table 3).

15
16 **Discussion**

17
18 This is the largest study to date to assess the value of the triggers for palliative care
19 involvement proposed by current palliative care policy guidance for individuals with
20 PNCs. There was evidence of high burden of triggers in the last 2 years of life for
21 patients with neurological conditions, with a rapid increase in the last 6 months. Four
22 factors explained a large proportion of the variance in the triggers indicating the
23 triggers could be grouped in fewer components. Different factors and triggers were

1 associated with survival from diagnosis and referral to palliative care services; this
2 was also the case when the associations were assessed for individual diagnoses. These
3 results indicate that the association of the triggers with survival is complex and that
4 different triggers may be more important in different PNCs.

5
6 The use of triggers appears to be valuable in predicting deterioration in the last 6 to 12
7 months of life. The commonest triggers were decline in physical function, complex
8 symptoms and dysphagia. These were found for all diagnoses. The frequency of these
9 triggers may reflect that they are the most burdensome issues for patients, but may
10 also reflect that the other triggers, especially weight loss and cognitive impairment are
11 less well assessed or documented. The total number of triggers increased as death
12 approached and there appears to be an exponential pattern as shown in the earlier
13 study (9). There is a rapid change in the numbers of triggers towards death and thus
14 monitoring the rate of change in the total number of triggers may be a useful
15 prognostic tool, indicating that the person may be in the last few months of life.

16
17 The four factors that explained the most variance in the last 6 months of life could be
18 categorised as factor 1: deterioration of physical function (which would include
19 deterioration in swallowing ability, development of significant complex symptoms,
20 and pain), factor 2: weight loss and respiratory symptoms, factor 3: recurrent
21 infections and cognitive impairment, and factor 4: aspiration. These are similar to the
22 factors identified in the previous analysis on a smaller sample (9). Despite the larger
23 sample in this study, the small Cronbach alphas indicate that the results should be

1 interpreted with caution. Current clinical understanding may not necessarily suggest
2 these groupings, and initially the expert group did report these triggers individually.
3 However the analyses in both studies have suggested similar factors and the
4 components do measure a large proportion of the variation in the data and therefore it
5 would seem that the triggers could be reduced to fewer components. Further studies
6 that collect the triggers data prospectively are now needed to reassess the factor
7 loading before implementing changes to practice.

8
9 The association between triggers and survival was complex. There was insufficient
10 evidence that the factors derived from the PCA were associated with survival from
11 diagnosis when all diagnoses were grouped together, however in the PD group factor
12 4 (aspiration) had a statistically significant association with survival from diagnosis
13 and for the PD plus group both factors 1 and 3. In terms of the individual triggers,
14 there was evidence when all diagnoses are grouped together that the total number of
15 triggers at 3 months was associated with survival from both diagnosis and palliative
16 care referral. Although there was evidence that as the number of episodes of weight
17 loss increased, the hazard of death increased when all the diagnoses were grouped
18 together, for the MND, PD and PD plus group other triggers had a significant
19 association with survival. This indicates that different triggers may be useful in aiding
20 prognostication for different conditions, however further research with larger samples
21 for each diagnostic group is required.

22
23 Limitations

1 Data collected as part of routine clinical practice was extracted for this study therefore
2 there is a risk of information bias due to inaccurate collection, interpretation or
3 documentation of triggers. To minimise bias at the data extraction phase detailed
4 guidance was provided, together with email / telephone support throughout the
5 process. In addition healthcare professionals who were aware of the clinical context
6 extracted data. This review focussed on triggers in the last two years of life and was
7 limited to patients known to palliative care services, thus these findings may not be
8 generalisable to all patients with PNCs. This should be addressed in future research..
9
10 This study provides evidence that the triggers for palliative care involvement
11 advocated by the NEoLCP, SPICT and Marie Curie Triggers for palliative care
12 guidance may be helpful in the assessment of patients with PNC and identifying
13 patients in the last few months of life. There is increasing evidence that palliative care
14 can be helpful in improving symptoms and quality of life (15, 16,17) and that the
15 involvement of SPC should be dependent on need rather than prognosis. However this
16 episodic approach is a challenge for SPC services (4, 18) and the use of triggers may
17 be able to help in both the identification of disease burden and prognostication that
18 death may be approaching, which would support the involvement of palliative care
19 with patients with PNC. It is essential however that the triggers suggested by experts
20 in the field are rigorously assessed and developed to ensure patients receive optimal
21 palliative care input. This study has helped to identify key areas for further
22 prospective research including how the triggers could potentially be categorised into
23 fewer components, how the rate of change of triggers is associated with survival and

1 which triggers are most useful for different PNC. We would also advocate patient and
2 carer involvement to determine which triggers for palliative care involvement warrant
3 further assessment.
4
5

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The authors have no conflict of interest to declare

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Table 1. Average number of each trigger in the last 2 years and 6 months of life and the proportion of patients with each trigger

Triggers	Average number of triggers in last 2 years of life Mean (SD)	Proportion of participants with the trigger in last 2 years of life Number (%)	Average number of triggers in last 6 months of life Mean (SD)	Proportion of participants with the trigger in last 6 months of life Number (%)
Deteriorating physical function	5.0 (4.0)	286 (96%)	2.9 (2.5)	267 (89%)
Dysphagia	2.5 (2.3)	258 (86%)	1.5 (1.5)	211 (70%)
Aspiration	0.8 (1.5)	119 (40%)	0.7 (0.1)	109 (36%)
Infection	0.8 (1.3)	123 (41%)	0.5 (0.9)	93 (31%)
Weight loss	1.2 (1.6)	168 (56%)	0.6 (0.9)	127 (42%)
Cognitive impairment	0.9 (2.1)	96 (32%)	0.5 (1.1)	75 (25%)
Significant complex symptoms	3.9 (5.2)	206 (69%)	2.3 (3.1)	182 (61%)
Pain	1.3 (2.3)	167 (56%)	0.8 (1.4)	133 (44%)
Respiratory symptoms	(1.0)	63 (21%)	0.3 (0.8)	42 (14%)

Table 2. Correlation matrix for each trigger in the last 6 months of life

	Decline in physical function	Dysphagia	Aspiration	Infection	Weight loss	Cognitive impairment
Decline in physical function	1					
Dysphagia	0.47 <0.001	1				
Aspiration	0.04 0.5	0.21 <0.001	1			
Infection	0.15 <0.01	0.01 0.9	-0.00 0.9	1		
Weight loss	0.32 <0.001	0.31 <0.001	0.02 0.8	0.09 0.1	1	
Cognitive impairment	0.08 0.2	0.11 0.06	-0.05 0.4	0.15 <0.01	0.07 0.2	1
Pain	0.29 <0.001	0.24 <0.001	0.13 <0.01	-0.05 0.4	0.01 0.8	0.01 0.9
Significant complex symptoms	0.54 <0.001	0.30 <0.001	0.01 0.8	0.09 0.1	0.19 0.001	0.06 0.3
Respiratory	0.19 0.001	0.20 <0.001	0.06 0.3	-0.04 0.5	0.23 <0.001	-0.07 0.2

Table 3. Summary of the principal component analysis using triggers in the last 6 months of life.

	Factor 1: Deterioration in physical function, dysphagia, significant complex symptoms and pain	Factor 2: Weight loss and respiratory symptoms	Factor 3: Recurrent infections and cognitive decline	
Pain	.76			
Significant complex symptoms	.74			
Decline in physical function	.73			
Dysphagia	.49			
Weight loss		.72		
Respiratory		.72		
Cognitive impairment			.73	
Infection			.71	
Aspiration				

Table 5. Cox regression analysis assessing the association of the factors derived from the principal component analysis with survival from diagnosis

Survival time	Explanatory variable	Motor neurone disease			Parkinson's disease			Parkin	
		Adjusted hazard ratio*	95% CI	P-value	Adjusted hazard ratio*	95% CI	P-value	Adjusted hazard ratio*	95%
From diagnosis	Factor 1	0.96	0.84, 1.09	0.5	0.79	0.49, 1.26	0.3	2.16	1.1
	Factor 2	1.04	0.90, 1.21	0.6	0.83	0.41, 1.70	0.6	0.86	0.5
	Factor 3	1.01	0.86, 1.18	0.9	1.30	0.83, 2.03	0.3	1.70	1.0
	Factor 4	0.97	0.81, 1.13	0.7	2.51	1.19, 5.32	<0.05	1.26	0.8
From palliative care referral	Factor 1	0.94	0.80, 1.12	0.5	0.58	0.33, 0.99	<0.05	1.38	0.6
	Factor 2	1.05	0.90, 1.22	0.6	0.63	0.36, 1.57	0.3	0.50	0.2
	Factor 3	1.00	0.85, 1.19	0.9	1.02	0.64, 1.64	0.9	2.49	1.3
	Factor 4	0.88	0.73, 1.05	0.2	2.47	1.06, 5.75	<0.05	2.06	1.2

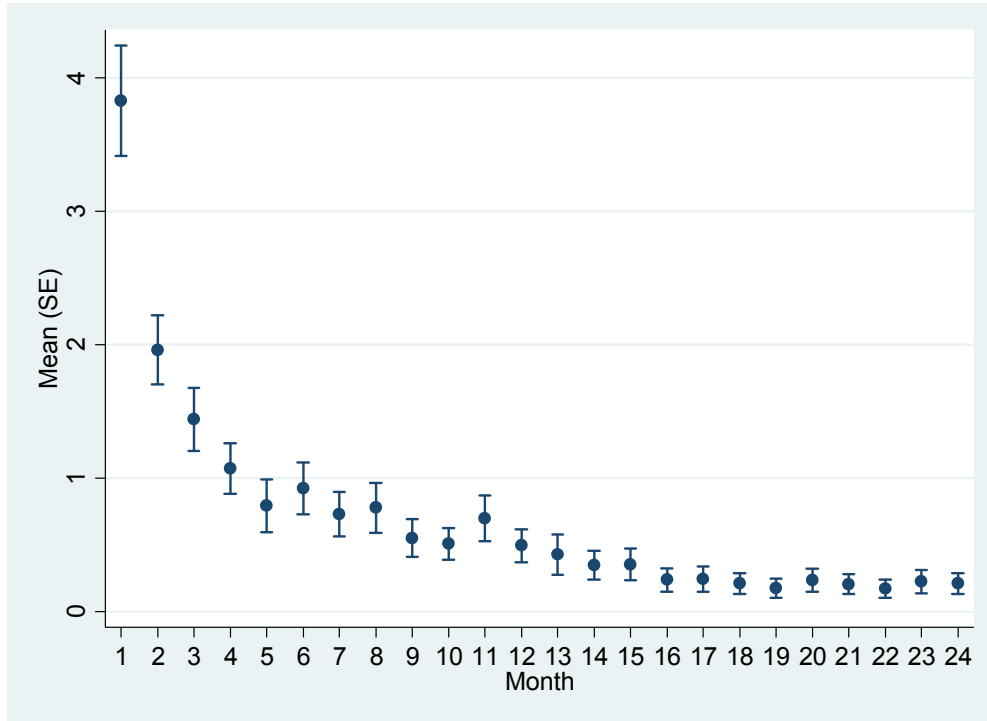
* Model adjusted for age, gender and number of comorbidities

Table 4.

Survival time	Explanatory variable	Hazard ratio	95% CI	P-value	Adjusted hazard ratio*	95% CI	P-value
From diagnosis	Factor 1	1.03	0.93, 1.15	0.5	0.96	0.86, 1.07	0.5
	Factor 2	1.11	0.99, 1.26	0.1	1.00	0.88, 1.15	0.9
	Factor 3	0.96	0.85, 1.09	0.6	1.05	0.92, 1.19	0.5
	Factor 4	1.06	0.94, 1.20	0.3	1.01	0.88, 1.14	0.9
From palliative care referral	Factor 1	0.87	0.76, 0.99	<0.05	0.86	0.75, 0.99	<0.05
	Factor 2	1.05	0.93, 1.19	0.4	1.03	0.89, 1.18	0.7
	Factor 3	0.99	0.86, 1.13	0.9	1.04	0.90, 1.20	0.6
	Factor 4	1.03	0.90, 1.19	0.7	0.99	0.85, 1.16	0.9

* Model adjusted for age, gender, diagnosis and number of comorbidities

Figure 1: Total number of triggers (any) by month (Mean and standard error)



Appendix Table 1: Mean number of triggers in the last 2 years of life per diagnosis (SD)

Triggers	MND ¹ N=173	PD ² N=50	PD Plus ³ N=36	MS ⁴ N=26	HD ⁵ N=7
Deteriorating physical function	5.2 (4.0)	5.2 (4.0)	6.4 (4.5)	2.8 (3.1)	2.3 (1.8)
Dysphagia	2.7 (2.3)	1.8 (1.4)	3.4 (3.3)	1.5 (1.8)	1.4 (0.8)
Aspiration	0.8 (1.3)	0.7 (1.3)	1.3 (2.3)	0.8 (1.0)	1.3 (2.0)
Infection	0.7 (1.2)	0.7 (1.3)	1.4 (1.6)	1.3 (1.4)	0.6 (1.1)
Weight loss	1.2 (1.4)	1.5 (2.2)	1.3 (1.6)	0.7 (1.7)	1 (0.8)
Cognitive impairment	0.6 (2.1)	1.5 (2.0)	1.0 (1.7)	1.2 (2.0)	2.0 (2.1)
Significant complex symptoms	4.1 (5.0)	2.8 (3.1)	5.6 (8.5)	3.0 (3.5)	1.6 (2.1)
Pain	1.5 (2.6)	1.0 (1.4)	1.5 (2.0)	1.4 (2.4)	0.3 (0.5)
Respiratory symptoms	0.5 (1.2)	0.2 (0.7)	0.06 (0.2)	0.08 (0.3)	0

¹ Motor Neurone Disease

² Parkinson’s disease

³ Parkinson Plus syndromes

⁴ Multiple sclerosis

⁵ Huntington’s disease

Appendix Table 2: Cox regression analysis assessing the association of individual triggers and the total number of triggers at 3, 6 and 12 months with (i) survival from diagnosis and (ii) survival from palliative care referral (all participants)

Survival time	Explanatory variable	Univariable hazard ratio	95% CI	P-value	Adjusted hazard ratio*	95% CI	P-value
From diagnosis	Age	0.997	0.987, 1.006	0.5	1.006	0.993, 1.019	0.4
	Gender	0.836	0.655, 1.067	0.2	1.100	0.833, 1.454	0.5
	Diagnosis			<0.0001			<0.0001
	Comorbidities	1.025	0.942, 1.115	0.6	1.081	0.988, 1.183	0.09
	Decline in physical function	1.013	0.987, 1.039	0.4	0.977	0.927, 1.029	0.4
	Dysphagia	1.069	1.014, 1.127	0.01	1.046	0.964, 1.136	0.3
	Aspiration	1.031	0.953, 1.114	0.4	0.968	0.883, 1.062	0.5
	Infection	0.971	0.884, 1.066	0.5	0.977	0.873, 1.093	0.7
	Weight loss	1.030	0.960, 1.104	0.4	1.012	0.911, 1.124	0.8
	Cognitive impairment	0.974	0.913, 1.038	0.4	1.001	0.939, 1.068	1.0
	Pain	1.016	0.964, 1.070	0.6	0.990	0.928, 1.057	0.8
	Significant complex symptoms	1.012	0.990, 1.035	0.3	0.998	0.960, 1.036	0.9
	Respiratory symptoms	1.093	0.964, 1.239	0.2	0.894	0.749, 1.067	0.2
	Total number of triggers	1.006	0.997, 1.015		-	-	-
	Number of triggers at 3 months	1.078	1.021, 1.139	<0.01	1.083	1.013, 1.158	<0.05
	Number of triggers at 6 months	1.042	0.971, 1.118	0.3	1.028	0.934, 1.132	0.6
	Number of triggers at 12 months	0.969	0.866, 1.085	0.6	0.973	0.851, 1.113	0.7
From palliative care	Age	1.014	1.003, 1.025	<0.05	1.019	1.005, 1.034	<0.05
	Gender	1.186	0.924, 1.521	0.2	1.109	0.834, 1.484	0.5

referral			1.524			1.475	
	Diagnosis			0.7			0.5
	Decline in physical function	0.988	0.958, 1.019	0.4	0.954	0.904, 1.007	0.09
	Dysphagia	1.024	0.972, 1.078	0.4	1.005	0.932, 1.084	0.9
	Aspiration	1.005	0.913, 1.107	0.9	0.993	0.895, 1.101	0.9
	Infection	1.046	0.943, 1.160	0.4	1.115	0.988, 1.259	0.08
	Weight loss	1.049	0.974, 1.130	0.2	1.125	1.015, 1.246	<0.05
	Cognitive impairment	0.954	0.899, 1.013	0.1	0.933	0.870, 1.001	<0.05
	Pain	0.961	0.907, 1.017	0.2	0.981	0.921, 1.045	0.6
	Significant complex symptoms	0.993	0.967, 1.021	0.6	1.012	0.973, 1.052	0.6
	Respiratory symptoms	1.100	0.963, 1.257	0.2	0.999	0.841, 1.187	1.0
	Total number of triggers	0.997	0.987, 1.007	0.5	-	-	-
	Number of triggers at 3 months	1.052	0.994, 1.114	0.08	1.099	1.030, 1.171	<0.01
	Number of triggers at 6 months	1.002	0.923, 1.087	1.0	0.977	0.879, 1.086	0.7
	Number of triggers at 12 months	0.895	0.800, 1.002	0.1	0.912	0.799, 1.041	0.2

* Model adjusted for age, gender, diagnosis and number of comorbidities

Appendix Table 3: Multivariable Cox regression for survival from diagnosis and triggers for patients with Motor Neuron Disease, Parkinson's Disease and Parkinson Plus syndromes

Explanatory variable	Motor neurone disease		Parkinson's disease		Parkinson's plus	
	Hazard ratio	95% CI	Hazard ratio	95% CI	Hazard ratio	95% CI
Age	1.006	0.991, 1.021	1.058	0.989, 1.131	0.984	0.860, 1.125
Gender	1.422	1.003, 2.015	0.366	0.131, 1.019	0.591	0.159, 2.197
Comorbidities	1.082	0.963, 1.216	1.143	0.880, 1.484	1.053	0.716, 1.550
Decline in physical function	0.973	0.911, 1.040	1.081	0.885, 1.321	0.964	0.725, 1.281
Dysphagia	1.045	0.944, 1.156	1.017	0.721, 1.435	1.081	0.756, 1.547
Aspiration	0.907	0.794, 1.036	2.079	1.314, 3.289	1.149	0.914, 1.444
Infection	0.862	0.733, 1.012	1.195	0.892, 1.601	1.727	1.035, 2.916
Weight loss	1.084	0.936, 1.257	0.826	0.633, 1.658	1.157	0.653, 2.051
Cognitive impairment	0.993	0.919, 1.073	1.210	0.883, 1.658	1.515	1.024, 2.241
Pain	0.957	0.881, 1.040	1.123	0.772, 1.635	1.078	0.645, 1.801
Significant complex symptoms	0.977	0.928, 1.028	0.831	0.673, 1.027	1.123	0.986, 1.279
Respiratory symptoms	0.905	0.743, 1.102	1.416	0.616, 3.252	0.840	0.003, 218.2
Number of triggers at 3 months	1.129	1.044, 1.222	1.289	0.985, 1.688	1.131	0.794, 1.613
Number of triggers at 6 months	1.059	0.938, 1.196	0.826	0.606, 1.127	0.511	0.272, 0.963
Number of triggers at 12 months	0.930	0.759, 1.140	0.663	0.383, 1.147	1.338	0.787, 2.274