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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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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: To develop an evidence base for the use of triggers for patients with progressive neurological disease.
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.
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:
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
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.
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.

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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.

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

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

Implications for practice, theory or policy?

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

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

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

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

restricted than for cancer patients (4). It has been suggested that this is due to the variability in the progression and prognosis of patients with neurological disease and the difficulty in recognising deterioration and that a patient is at the end of life (4,5).

The National End of Life Care (NEoLC) Programme framework for end of life care in long term neurological conditions suggested possible triggers for the identification of the end of life phase (the last 6-12 months) in this patient population. These 'triggers' are characteristics or events which have a significance within the disease progression, are readily recognised and can be easily used clinically. The triggers suggested included swallowing problems, recurring infection, marked decline in functional status, first episode of aspiration pneumonia, cognitive difficulties, weight loss and significant complex symptoms (5). The use of such triggers has also been advocated by the Supportive and Palliative Care Indicators Tool (SPICT) (6) and the Marie Curie Triggers for Palliative Care (7) guidance which have suggested that triggers for palliative care involvement are used by service providers to improve palliative care access for such patients.

The triggers suggested by the NEoLC programme and other guidance are based on expert consensus and there has been little research in this area. It is essential that a robust evidence base is developed to inform and evaluate new palliative care policy, as was illustrated in the review of the Liverpool Care Pathway (LCP) (8). A small study from one centre evaluated the triggers suggested for PNCs and found four symptom components explained 76.8% of the variance (9). These triggers were rapid

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

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

Methods

Study design and setting

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

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

Participants

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

Data sources

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

Variables

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

this was considered by the APM Neuro-SIF as a potential important trigger for palliative care involvement in PNC, and in particular MND.

Analysis

Descriptive data is summarised by the mean (standard deviation (SD)) or number (%). Principal component analysis (PCA) was used to assess the correlation between the triggers and to identify common components and therefore whether the triggers could be reduced to fewer components. In this type of analysis the correlation between parameters (triggers) is attributed to their common dependence on independent entities called 'factors'. The coefficients that link parameters to factors are called 'factor loadings'; the number of factors is chosen to be as small as possible but large enough to account for most of the variation within the data. PCA was conducted using data from the last six months as there was evidence that the number of triggers increased rapidly after this point and to optimise the number of complete cases. It was decided *a-priori* that the number of factors in the varimax rotation would be based on the number of eigenvalues >1.0 in the PCA. We adopted one common and conventional rule of thumb to consider 'factor loadings' of 0.40 or larger to be 'high'. Tests of multicollinearity (Bartlett's test of sphericity $p<0.05$) and sampling adequacy (Kaiser-Meyer-Olkin (KMO)) were undertaken to check the analysis was appropriate. The internal consistency and reliability of the factors was assessed using Cronbach's α. The least squares regression approach was used to calculate the factor scores, which are standardized to a mean of zero. The factor scores may then be used as variables in subsequent modelling (10).

Univariable and multivariable (adjusted for age, gender, diagnosis and comorbidities) Cox regression analyses were used to assess the association of survival from (i) diagnosis and (ii) referral, and:

a. factor scores determined by the PCA,

b. individual triggers and the number of triggers at 3, 6 and 12 months.

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

Results

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

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

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

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

Principal component analysis

Factor analysis yielded four separate factors that explained 64% of the total variance in the data set when the eigenvalue =1 criterion was used. Using data from the last 6 months of life, the correlation matrix is shown in Table 2. Bartlett's test of sphericity ($\chi 2$=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

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

Survival and factor scores:

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

Survival and individual triggers:

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

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

Association between triggers and survival for different diagnoses

Survival and factor scores:

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

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

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

Survival and individual triggers:

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

Discussion

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

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

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

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

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

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

Limitations

Data collected as part of routine clinical practice was extracted for this study therefore there is a risk of information bias due to inaccurate collection, interpretation or documentation of triggers. To minimise bias at the data extraction phase detailed guidance was provided, together with email / telephone support throughout the process. In addition healthcare professionals who were aware of the clinical context extracted data. This review focussed on triggers in the last two years of life and was limited to patients known to palliative care services, thus these findings may not be generalisable to all patients with PNCs. This should be addressed in future research..

This study provides evidence that the triggers for palliative care involvement advocated by the NEoLCP, SPICT and Marie Curie Triggers for palliative care guidance may be helpful in the assessment of patients with PNC and identifying patients in the last few months of life. There is increasing evidence that palliative care can be helpful in improving symptoms and quality of life (15, 16,17) and that the involvement of SPC should be dependent on need rather than prognosis. However this episodic approach is a challenge for SPC services (4, 18) and the use of triggers may be able to help in both the identification of disease burden and prognostication that death may be approaching, which would support the involvement of palliative care with patients with PNC. It is essential however that the triggers suggested by experts in the field are rigorously assessed and developed to ensure patients receive optimal palliative care input. This study has helped to identify key areas for further prospective research including how the triggers could potentially be categorised into fewer components, how the rate of change of triggers is associated with survival and

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

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Declaration of conflicting interests

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

		Motor neurone disease			Parkinson's disease			Parkin	
Survival time	Explanatory variable	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

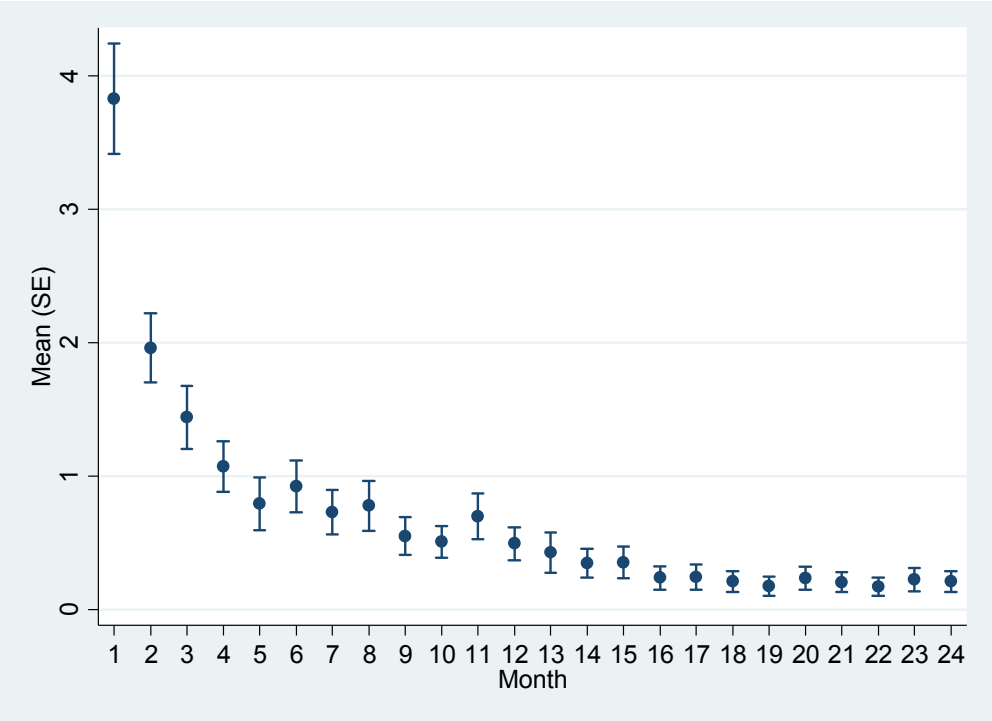
***** Model adjusted for age, gender and number of comorbidities

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,	0.2	1.109	0.834,	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

	Motor neurone disease		Parkinson's disease		Parkinson's plus	
Explanatory variable	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