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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:<br/>Factor 1 – Deterioration in physical function, dysphagia, significant complex symptoms and pain<br/>Factor 2 – Weight loss and respiratory symptoms<br/>Factor 3 – Recurrent infections and cognitive decline<br/>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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**Palliative care triggers in progressive neurodegenerative conditions: a multi-centre retrospective case record review and principal component analysis**

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1 **Abstract**

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

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

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

8 Setting/participants: 12 specialist palliative care units across the UK provided data  
9 from 300 patients: mean patient age 70 years, 50% male, diagnoses included Motor  
10 Neurone Disease 58%, Parkinson's disease 17% and Parkinson's plus syndromes  
11 12%.

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

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

18 Factor 2 – Weight loss and respiratory symptoms

19 Factor 3 – Recurrent infections and cognitive decline

20 Factor 4 – Aspiration pneumonia.

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

1  
2 **Conclusions:** This study demonstrates that there is a high burden of triggers in the  
3  
4 last months and years of life and that these could potentially be reduced to fewer  
5  
6 components. Prospective studies assessing which triggers are useful for different  
7  
8 conditions are now required.  
9

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13 **Key Words**

14  
15 Triggers, palliative care, neurodegenerative disease, survival analysis, Motor Neuron  
16  
17 Disease, Parkinson's Disease  
18

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21  
22 **What is already known about the topic?**

23  
24 The use of triggers to identify the end of life phase and need for palliative care  
25  
26 involvement for patients with progressive neurological conditions has been advocated  
27  
28 in several policy documents.  
29

30  
31  
32 The triggers suggested are based on expert consensus.  
33

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35  
36  
37 There is a need to build an evidence base to inform and evaluate such policy  
38  
39 recommendations.  
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43 **What this paper adds?**

44  
45 The average number of triggers in the last 2 years of life was 17, with an exponential  
46  
47 increase in the last 6 months of life.  
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2 1 Four factors explained 64% of the variance in the triggers.  
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6 3 Different triggers were associated with survival from diagnosis and referral to  
7  
8 4 palliative care across all participants, and for different neurological conditions.  
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13 6 **Implications for practice, theory or policy?**  
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15 7 The high burden of triggers in the last few months of life indicates the need for  
16 8 palliative care involvement for this patient group.

17 9  
18 10 The correlation between triggers suggests the triggers could be reduced to fewer  
19 11 components.

20 12  
21 13 There is evidence that different triggers may help prognostication over different time  
22 14 frames and for different conditions.  
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**Introduction**

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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.

3

#### 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.

8

#### 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.

15

#### 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.

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9 4 *Analysis*

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

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4 2 Univariable and multivariable (adjusted for age, gender, diagnosis and comorbidities)  
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6 3 Cox regression analyses were used to assess the association of survival from (i)  
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8 4 diagnosis and (ii) referral, and:  
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10 a. factor scores determined by the PCA,  
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12 b. individual triggers and the number of triggers at 3, 6 and 12 months.  
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17 8 The Cox regression analyses for survival from diagnosis were repeated according to  
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19 9 whether the participants were diagnosed with MND, PD or PD plus. Assessment of  
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21 10 the other diagnoses was not possible as the number of participants with the diagnoses  
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23 11 was insufficient. A p-value of <0.05 was considered to indicate statistical significance  
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25 12 and all analyses were undertaken on STATA (v14.0)  
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## 30 14 **Results**

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34 16 In total 300 clinical records were reviewed retrospectively. The mean age was 70  
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36 17 years (range 35 to 98), 50% were male and 92% were White. The main diagnoses  
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38 18 were MND (58%), PD (17%), PD Plus (12%), MS (9%), and HD (2%). The majority  
39  
40 19 had co-morbidities (76%), with 46% having two or more comorbidities.  
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## 44 45 21 **Frequency of triggers for palliative care involvement in PNC in the last 2 years** 46 47 22 **and 6 months of life**

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2 1 The average number of total triggers over the last 2 years of life was 16.7 (SD 12.7)  
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4 2 and in the last 6 months 10.0 (SD 7.4). Table 1 demonstrates that the most frequent  
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6 3 triggers in both the last 2 years and 6 months of life was deteriorating physical  
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8 4 function (2 years: 5.0 (SD 4.0), 6 months: 2.9 (SD 2.5)) followed by significant  
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10 5 complex symptoms (2 years: 3.9 (SD 5.2), 6 months: 2.3 (SD 3.1)) and dysphagia (2  
11  
12 6 years: 2.5 (SD 2.3), 6 months: 1.5 (SD 1.5)). The same pattern was seen when trigger  
13  
14 7 frequency was assessed per diagnosis for patients with MND, PD, and PD Plus  
15  
16 8 (Appendix Table 1). However for those with MS significant complex symptoms (3.0  
17  
18 9 (SD 3.5)) were slightly more frequent than deteriorating physical function (2.8 (SD  
19  
20 10 3.1)), and for the seven participants diagnosed with Huntington's disease cognitive  
21  
22 11 impairment was the second most frequent trigger (2.0 (SD 2.1)).  
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28 13 In the last 2 years of life just over half of patients had documented evidence of weight  
29  
30 14 loss (56%) and pain (56%), and in the last 6 months the figures were just under half  
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32 15 (weight loss 42%; pain 44%). Figure 1 illustrates the trend in the total number of  
33  
34 16 triggers according to months prior to death, this demonstrates an exponential increase  
35  
36 17 in the number of triggers over time, with a rapid increase in the last 6 months of life. .  
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### 41 19 **Principal component analysis**

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43 20 Factor analysis yielded four separate factors that explained 64% of the total variance  
44  
45 21 in the data set when the eigenvalue =1 criterion was used. Using data from the last 6  
46  
47 22 months of life, the correlation matrix is shown in Table 2. Bartlett's test of sphericity  
48  
49 23 ( $\chi^2=349$ , degree of freedom=36,  $p<0.0001$ ) indicated that the correlation between the  
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1 variables were sufficiently large for PCA. The KMO measure of sampling adequacy  
2 was 0.68, which can be interpreted as the degree of common variance among the  
3 variables, and verified the sampling adequacy of the analysis.

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

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

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

## 20 21 **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: 14, 34).. 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: 4, 16)..

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).

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

#### 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

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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.  
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For Peer Review

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14

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16 The authors have no conflict of interest to declare

17

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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**

| <b>Triggers</b>                        | <b>Average number of triggers in last 2 years of life<br/>Mean (SD)</b> | <b>Proportion of participants with the trigger in last 2 years of life<br/>Number (%)</b> | <b>Average number of triggers in last 6 months of life<br/>Mean (SD)</b> | <b>Proportion of participants with the trigger in last 6 months of life<br/>Number (%)</b> |
|--|---|---|--|--|
| <b>Deteriorating physical function</b> | 5.0 (4.0)   | 286 (96%)   | 2.9 (2.5)  | 267 (89%)  |
| <b>Dysphagia</b>                       | 2.5 (2.3)   | 258 (86%)   | 1.5 (1.5)  | 211 (70%)  |
| <b>Aspiration</b>                      | 0.8 (1.5)   | 119 (40%)   | 0.7 (0.1)  | 109 (36%)  |
| <b>Infection</b>                       | 0.8 (1.3)   | 123 (41%)   | 0.5 (0.9)  | 93 (31%)   |
| <b>Weight loss</b>                     | 1.2 (1.6)   | 168 (56%)   | 0.6 (0.9)  | 127 (42%)  |
| <b>Cognitive impairment</b>            | 0.9 (2.1)   | 96 (32%)  | 0.5 (1.1)  | 75 (25%)   |
| <b>Significant complex symptoms</b>    | 3.9 (5.2)   | 206 (69%)   | 2.3 (3.1)  | 182 (61%)  |
| <b>Pain</b>                            | 1.3 (2.3)   | 167 (56%)   | 0.8 (1.4)  | 133 (44%)  |
| <b>Respiratory symptoms</b>            | (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                    | <b>0.47</b><br><0.001        | 1                     |                      |                      |                       |                      |
| Aspiration                   | <b>0.04</b><br>0.5           | <b>0.21</b><br><0.001 | 1                    |                      |                       |                      |
| Infection                    | <b>0.15</b><br><0.01         | <b>0.01</b><br>0.9    | <b>-0.00</b><br>0.9  | 1                    |                       |                      |
| Weight loss                  | <b>0.32</b><br><0.001        | <b>0.31</b><br><0.001 | <b>0.02</b><br>0.8   | <b>0.09</b><br>0.1   | 1                     |                      |
| Cognitive impairment         | <b>0.08</b><br>0.2           | <b>0.11</b><br>0.06   | <b>-0.05</b><br>0.4  | <b>0.15</b><br><0.01 | <b>0.07</b><br>0.2    | 1                    |
| Pain                         | <b>0.29</b><br><0.001        | <b>0.24</b><br><0.001 | <b>0.13</b><br><0.01 | <b>-0.05</b><br>0.4  | <b>0.01</b><br>0.8    | <b>0.01</b><br>0.9   |
| Significant complex symptoms | <b>0.54</b><br><0.001        | <b>0.30</b><br><0.001 | <b>0.01</b><br>0.8   | <b>0.09</b><br>0.1   | <b>0.19</b><br>0.001  | <b>0.06</b><br>0.3   |
| Respiratory                  | <b>0.19</b><br>0.001         | <b>0.20</b><br><0.001 | <b>0.06</b><br>0.3   | <b>-0.04</b><br>0.5  | <b>0.23</b><br><0.001 | <b>-0.07</b><br>0.2  |

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

|                              | <b>Factor 1:</b><br>Deterioration in physical function, dysphagia, significant complex symptoms and pain | <b>Factor 2:</b><br>Weight loss and respiratory symptoms | <b>Factor 3:</b><br>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% |
| <b>From diagnosis</b>                | 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 |
| <b>From palliative care referral</b> | 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 |

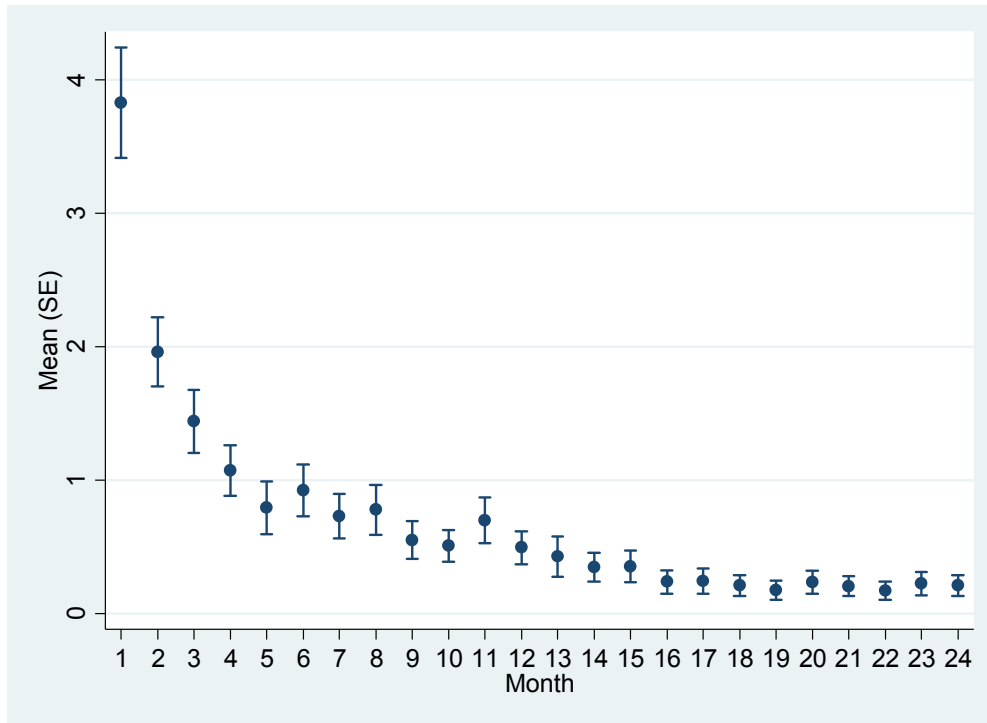
\* Model adjusted for age, gender and number of comorbidities

Table 4.

| Survival time                        | Explanatory variable | Hazard ratio | 95% CI     | P-value | Adjusted hazard ratio* | 95% CI     | P-value |
|--------------------------------------|----------------------|--------------|------------|---------|------------------------|------------|---------|
| <b>From diagnosis</b>                | 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     |
| <b>From palliative care referral</b> | 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)**

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

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<sup>1</sup> Motor Neurone Disease

<sup>2</sup> Parkinson's disease

<sup>3</sup> Parkinson Plus syndromes

<sup>4</sup> Multiple sclerosis

<sup>5</sup> 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     |

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