*Neurology Asia 2022; 27(4) : 883 – 889*

# A simple and rapid focal seizure screening tool in resource-limited setting

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### *Abstract*

*Background & Objective:* A substantial proportion of patients were managed by general clinicians in resource-limited settings. Therefore, we aim to develop a simple and rapid focal seizure screening tool that can assist non-neurologists in seizure classification. *Methods:* We conducted a self-administered qualitative questionnaire study on seizure manifestation developed based on the validated comprehensive questionnaires by Reutens *et al*. for clinical diagnosis of seizures. Logistic regression analyses were conducted to determine the features of seizure which form the items of a focal seizure screening tool. A receiver operating characteristic (ROC) curve analysis was conducted to determine the optimal cut-off score. *Results:* Among the 199 subjects, 145 (73%) had focal seizures. Three categories of symptoms, i.e., (i) aura (fear, déjà vu, and epigastric aura), (ii) unilateral motor phenomena, and (iii) oral automatism, are significantly associated with the diagnosis of focal seizure. The logistic regression model containing these 3 items / features was statistically significant, $\chi 2$ (3, N=199) = 22.93, $p<0.001$, and correctly classified 71.4% of cases. A focal seizure screening tool was developed by assigning a score of 1 to each category of symptoms. The area under the curve of ROC curve is 0.706 (95% CI: 0.629-0.783), $p<0.001$. A score of ≥2 is the most optimal cut-off with a sensitivity of 50.3%, specificity of 85.2%, positive predictive value (PPV) of 91.0%, and negative predictive value (NPV) of 41.8%. *Conclusion:* A simple and rapid self-administered focal seizure screening tool was established with high specificity and PPV.

*Keywords:* Focal seizure, seizure classification, screening tool, self-administered, general clinicians, resource-limited setting

## INTRODUCTION

The lifetime prevalence of epilepsy is 0.78 per 1,000 persons in Malaysia.[1] Only around 30% of epilepsy patients are managed by neurologists, while a much larger proportion are managed by general physicians and medical officers due to the low neurologist-to-patient ratio in Malaysia[2], as well as many other resource-limited settings (low-middle-income countries). Seizure type classification could be challenging for these clinicians who lack experience and training in the diagnosis and management of epilepsy. Inaccurate and delayed diagnosis may result in inappropriate anti-seizure medications (ASMs). This could lead to a low seizure remission rate among epilepsy patients and delay in referral to higher level epilepsy care centres.[2]

Since the emergence of artificial intelligence in healthcare, many deep learning models had been developed to classify seizures. In addition, many web-based algorithms such as EpiPick[3] were developed to help physicians in ASM selection based on seizure type. However, most of the available ASM selection tools require detailed seizure semiology which were frequently not well described or observed by the patient or witness because of anxiety. Thus, the complexity and usability of algorithms in other hospitals or countries require further validation in an external cohort.[3]

In this study, instead of solely depending on the clinician's history taking, we have designed a questionnaire that can be fully self-administered by the patient and/or witness. Secondly, we have focused only on the ability to differentiate focal onset seizures from generalised/undetermined onset, with two main implications. Firstly, certain ASMs that are effective in focal onset

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Date of Submission: 22 July 2022; Date of Acceptance: 20 September 2022
https://doi.org/10.54029/2022xsp

seizures may aggravate other seizure types such as carbamazepine. Therefore, one of the most important determinants in ASMs selection would be deciding whether the seizures are focal onset. Secondly, the need for further investigations especially magnetic resonance imaging (MRI) of the brain to determine the aetiology of epilepsy is more urgent in those with focal onset seizures. We aimed to develop a simple and rapid focal seizure screening model to aid general clinicians in seizure classification.

## METHODS

This was a cross-sectional study conducted at the University Malaya Medical Centre (UMMC), Kuala Lumpur, Malaysia. This study was approved by the medical ethics committee of UMMC (reference number: 872.6) and written consent was obtained from all participants.

Consecutive adult patients who had outpatient electroencephalograms (EEGs) at the UMMC EEG laboratory were recruited. The inclusion criteria were: (i) adults with an age of ≥18 years, and (ii) diagnosed with epilepsy by a neurologist. The exclusion criteria were: (i) patients with seizure mimics e.g., syncope, psychogenic non-epileptic attack, metabolic disorders, stroke, transient ischaemic attack, migraine, and sleep disorders; and (ii) patients without a definitive diagnosis of seizure or epilepsy being established by a neurologist.

A self-administered 33-item seizure questionnaire (Appendix 1) was developed based on the validated comprehensive questionnaires by Reutens *et al*. for clinical diagnosis of seizures.[4] The questionnaire consisted of seizure presentation in the past, before, during and after a seizure. Each item had a choice of yes, no, and uncertain. All participants answered the seizure questionnaire based on the patient's observation if the patient had no impaired awareness, and/or witness account.

### *Operational classification of seizure types*

Seizure types were classified as focal, generalised or undetermined onset according to the 2017 operational classification by the International League Against Epilepsy[5] based on seizure semiology, EEG, and brain MRI (if available). The EEGs were reported anonymously by a neurologist, without any knowledge of the subjects. For screening tool development, the seizure types were reclassified as focal and non-focal in statistical analysis.

### *Statistical analysis*

Statistical Package for the Social Sciences (SPSS) for Windows version 28.0 (IBM Corporation, Armonk, NY, USA) was employed in the analyses of our real-world data. Descriptive data were presented as mean and standard deviation (SD) for continuous variables, and numbers with percentages for nominal and categorical variables. For comparison between focal versus non-focal onset seizures, the (i) independent sample t-test was used for continuous variables, while (ii) Pearson's chi-square and Fisher's exact test were used for the analyses of categorical variables when appropriate. A two-sided P value of $<0.05$ was considered statistically significant. Logistic regression analysis was conducted to identify the items significantly associated with focal seizure.

### *Screening model*

All significant items were assigned a score based on the logistic regression result. A receiver operating characteristic (ROC) curve analysis was conducted to (i) assess the accuracy of the screening model using the area under the curve (AUC), and (ii) determine the optimal cut-off score. Sensitivity, specificity, positive predictive values (PPV), and negative predictive values (NPV) with each of these scores were calculated.

## RESULTS

A total of 199 subjects were recruited, of which 104 (52%) were males, with a mean age of seizure onset of 18.7±13.3 years, and 145 (73%) had focal seizures.

### *Factors associated with focal seizures*

Four groups of features were significantly more commonly seen in the group with focal seizures - (i) preictal warning, blurred vision, and palpitations, (ii) aura of fear, (iii) unilateral eye deviation and tonic limb movement, and (v) oral automatism. (Table 1)

For ease of analysis, we have regrouped these factors into three main categories.

I Aura: Besides fear (item 15), déjà vu and epigastric sensation (items 14 and 20) were included in this category because of the near significant *p*-value ($<0.1$), which was limited by the small sample size. Preictal warning, blurred vision and palpitations were excluded because of their nature of being common symptoms in syncope.

**Table 1: Cohort with focal seizure versus cohort with other seizure types (N=199)**

| Items | Focal seizure (n=145), N (%) | Others (n=54), N (%) | *p*-value |
|---|---|---|---|
| **Demographic characteristics** | | | |
| Gender (Male) | 80 (55) | 24 (44) | 0.178 |
| 1. Onset age (years) | 19.4 ± 13.4 | 16.6 ± 13.1 | 0.192 |
| **Past History** | | | |
| 2. Blank spells or spells in which you "switch off or go off the airwaves" | 59 (41) | 28 (52) | 0.158 |
| 3. Spells in which you twitch or jerk, especially just after waking up | 46 (32) | 15 (28) | 0.591 |
| 4. Childhood seizure | 49 (34) | 15 (28) | 0.419 |
| 5. Family history of seizure | 29 (20) | 15 (28) | 0.240 |
| 6. Head injury that made you unconscious | 35 (24) | 7 (13) | 0.086 |
| 7. Febrile episode that made you unconscious | 31 (21) | 10 (19) | 0.642 |
| **Seizure timing** | | | |
| 8. Time when most seizures occur | | | |
| a. Early morning | 12 (9) | 21 (39) | <0.001 |
| b. Daytime | 49 (34) | 10 (19) | |
| c. Early sleep | 21 (14) | 5 (9) | |
| d. Late sleep (after 12am) | 22 (15) | 7 (13) | |
| e. No specific time | 41 (28) | 11 (20) | |
| **Preictal** | | | |
| 9. Warning (aura) | 96 (66) | 18 (33) | <0.001 |
| 10. Dizziness | 68 (47) | 17 (31) | 0.051 |
| 11. Blurred vision | 52 (36) | 10 (19) | 0.019 |
| 12. Palpitations | 54 (37) | 9 (17) | 0.006 |
| **Ictal** | | | |
| 13. "Go blank" or lose awareness of your surroundings during the event | 102 (70) | 32 (59) | 0.138 |
| 14. A feeling of being in a dream or in an unusually strange or familiar place | 43 (30) | 9 (17) | 0.064 |
| 15. Fear | 45 (31) | 6 (11) | 0.004 |
| 16. See or hear things that are not real | 25 (17) | 8 (15) | 0.682 |
| 17. Unusual smells or tastes | 17 (12) | 3 (6) | 0.290 |
| 18. Any pins and needles, electric shocks, tingling, or other changes in sensation | 34 (23) | 8 (15) | 0.184 |
| 19. Objects or sounds in the room appear distorted or altered. For example, do sounds seem nearer or farther away or objects seem shrunken or magnified? | 22 (15) | 5 (9) | 0.356 |
| 20. Funny feeling in your tummy | 29 (20) | 5 (9) | 0.090 |
| 21. Eye unilateral deviation | 22 (15) | 2 (4) | 0.027 |
| Eye uprolling | 53 (37) | 30 (56) | 0.016 |
| 22. Head turning | 46 (32) | 14 (26) | 0.428 |
| 23. Bilateral tonic | 52 (36) | 22 (41) | 0.527 |

| | | | |
|---|---|---|---|
| Unilateral tonic | 33 (23) | 4 (7) | 0.013 |
| 24. Apnoea | 20 (14) | 8 (15) | 0.854 |
| 25. Unilateral clonic | 52 (36) | 12 (22) | 0.067 |
| Bilateral clonic | 49 (34) | 26 (48) | 0.063 |
| 26. Blink / eyelid twitching | 38 (26) | 17 (31) | 0.459 |
| 27. Smacking of the lips, licking of the lips, chewing, swallowing, or laughing | 55 (38) | 10 (19) | 0.009 |
| 28. Picking at or fiddling with things, walking, or making stepping or bicycling movements | 33 (23) | 8 (15) | 0.218 |
| 29. Speech | 29 (20) | 5 (9) | 0.091 |
| 30. Shouting | 30 (21) | 14 (26) | 0.429 |
| 31. Tongue biting | 63 (43) | 29 (54) | 0.197 |
| 32. Incontinence | 40 (28) | 12 (22) | 0.444 |
| **Postictal** | | | |
| 33. Postictal confusion/drowsiness | 118 (81) | 40 (74) | 0.257 |
| **Categories** | | | |
| I Aura (any of items 14, 15 and 20) | 80 (55) | 17 (31) | 0.003 |
| II Unilateral motor phenomena (any of items 21, 23 and 25) | 77 (53) | 16 (30) | 0.003 |
| III Oral automatism (item 27) | 55 (38) | 10 19) | 0.009 |

II Unilateral motor phenomena: In addition to unilateral eye deviation and tonic limb movement (items 21 and 23), unilateral clonic limb movement (item 25) was included because of its near significant *p*-value (<0.1).

III Automatism: Only oral automatism (item 27) was included.

*Logistic Regression*

A logistic regression model was performed to determine the items significantly associated with focal seizure classification. (Table 2) The model contained three independent variables (aura, unilateral motor phenomena and automatism). The full model containing all of these items was statistically significant, $\chi 2$ (3, N = 199) = 22.93, $p < 0.001$, indicating that the model was able to distinguish between respondents with and without focal seizures. The model as a whole explained between 10.9% (Cox and Snell R square) and 15.8% (Nagelkerke R squared) of the variance in focal seizure classification, and correctly classified 71.4% of cases.

*Focal seizure screening tool*

A focal seizure screening tool was developed by assigning a score of 1 to each category based on equal Exp(B) in the logistic regression model. (Table 3) This score ranged from 0 to 3.

*Receiver operating characteristic (ROC) curve analysis*

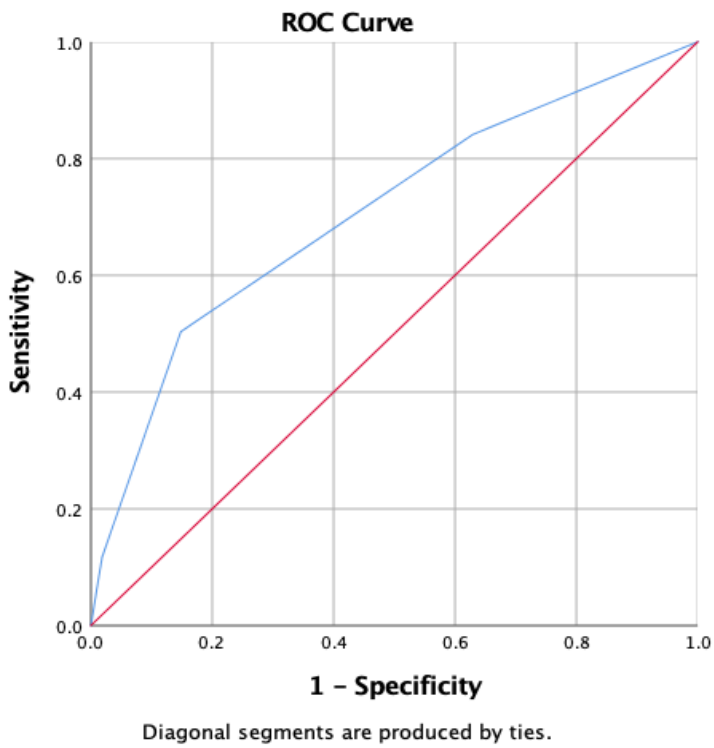
A ROC curve was constructed based on the data of focal seizure scores and actual diagnosis of focal seizure. (Figure 1) The accuracy of this screening

**Table 2: Logistic regression analysis of factors related to focal seizure**

| | B | S.E. | Wald | df | Sig. | Exp(B) | 95% C.I. for EXP(B) | |
|---|---|---|---|---|---|---|---|---|
| Aura (1) | 0.905 | 0.349 | 6.729 | 1 | 0.009 | 2.472 | 1.248 | 4.898 |
| Unilateral motor semiology (1) | 0.922 | 0.353 | 6.822 | 1 | 0.009 | 2.515 | 1.259 | 5.023 |
| Oral automatism (1) | 0.977 | 0.403 | 5.89 | 1 | 0.015 | 2.658 | 1.207 | 5.853 |
| Constant | -0.049 | 0.266 | 0.035 | 1 | 0.853 | 0.952 | | |

**Table 3: Scoring for focal seizure**

| For patient or eyewitness | For clinician | Score |
|---|---|---|
| Aura (any of the following)<br>– During the event, do you feel like being in a dream or an unusually strange or familiar place?<br>– During the event, do you have intense fear?<br>– During the event, funny feeling in your tummy? | – Déjà vu or Jamais Vu<br>– Aura of fear<br>– Epigastric aura | 1 |
| Unilateral motor phenomena (any of the following)<br>– During the event, did your (the patient's) eyes look to the left or right?<br>– During the event, did you (the patient) have arm or leg stiffness on one side of the body?<br>– During the event, did you (the patient) have jerking or twitching movements of the face, arm, or leg on one side of the body? | – Eye deviation<br>– Focal tonic seizure<br>– Focal clonic seizure | 1 |
| Oral automatism<br>– During the event, did you (the patient) have smacking of the lips, licking of the lips, chewing, swallowing, or laughing? | – Oral automatism | 1 |
| **Total** | | **3** |




| Positive if greater than or equal to | Sensitivity | 1 – Specificity |
|---|---|---|
| -1.0 | 1.000 | 1.000 |
| 0.5 | 0.841 | 0.630 |
| 1.5 | 0.503 | 0.148 |
| 2.5 | 0.117 | 0.019 |
| 4.0 | 0.000 | 0.000 |

Figure 1. ROC curve and coordinates of the focal seizure screening model.

model, in the form of AUC, is 0.706 (95% CI: 0.629 - 0.783), $p<0.001$. A score of ≥1.5, hence a score of ≥2 in the actual application, is determined to be the most optimal cut-off with a sensitivity of 50.3%, specificity of 85.2%, positive predictive value (PPV) of 91.0%, and negative predictive value (NPV) of 41.8%. (Table 4)

## DISCUSSION

We developed a simple screening model to differentiate focal from generalized and unknown onset seizure types in this study. This model could be self-administered, which allows patients or non-medically trained witnesses to report symptoms suggestive of focal seizures. In addition, it is simplified to three items to assist the general clinicians in deciding the likelihood of a seizure being focal onset.

### *Item selection*

We excluded preictal symptoms such as blurred vision ($p$=0.06) and palpitation ($p$=0.019) into the model as these are frequently seen in non-epileptic events such as syncope, although there were more frequently seen in the focal seizures.[6,7] We did not observe a significant difference in the frequencies of blank stare or other auras, such as olfactory, auditory, visual and somatosensory, between focal seizures and others. These symptoms could be too brief and subtle to be noticed by the patient or witnesses, or too complex to be reported and often requires careful clerking and confirmation by the clinicians. In contrast to the aforementioned aura, focal motor symptoms such as eye deviation, unilateral tonic or clonic movement were easily noticed by patients or witnesses. Oral automatism was commonly reported or noticed in those with focal seizures; however, limb automatism could be too complex and bizarre to the witnesses. Furthermore, perception of limb automatism by some patients and/or carers might not be accurate as post-ictal confusion could probably be misinterpreted as limb automatism. Whereas, certain symptoms could be present in both focal and generalized seizures, such as blank staring in absence seizures as well as in focal seizures, and thus have less discriminating value.

The difference in the reported time when most seizures occur among the 2 groups was statistically significant. The focal seizure group reported higher proportion of seizure occurring during daytime or with no specific time, while the group with other seizure types reported higher proportion of seizures occurring in the early morning. The later may be explained by the features of juvenile myoclonic epilepsy, a generalized epilepsy syndrome with recurrent generalized onset seizures (hence classified under the group with other seizure types in this study) commonly occurring shortly after waking up from sleep. However, such reported time when most seizures occur may be too complex, heterogeneous, and not specific to suggest a diagnosis of focal seizures.

### *Selection of the cut-off score*

Our focal seizure screening model showed that the specificity of a score of 2 was 85.2% with a PPV of 91.0%. This high specificity and PPV were desirable. For patients with focal seizures, carbamazepine will be the preferred ASMs, especially in most resource-limited countries because of its lower cost. However, at the same time, carbamazepine is known to have a risk of serious cutaneous adverse reactions, especially in the Southeast Asian population. Thus, a high specificity in our model will reduce the chance of carbamazepine being given to someone whose seizures are not focal and causing unnecessary serious reactions. Although the sensitivity of 50.3% in this model is relatively low, the seizure type can still be revised to focal onset if (i) any focal abnormality is detected on subsequent investigations such as EEG and MRI brain, or (ii) a focal semiology is witnessed or reported.

On the other hand, if the score is 1, the sensitivity is high (84%), which indicates the need for further EEG or neuroimaging evaluations. Furthermore, if the score is 2 (specificity = 85.2%, PPV = 91.0%) or 3 (specificity = 98.1%, PPV =

**Table 4: Sensitivity, Specificity, PPV and NPV of respective score as cut-off**

| Score | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|
| 1 | 84.1 | 37.0 | 78.2 | 46.5 |
| 2 | 50.3 | 85.2 | 91.0 | 41.8 |
| 3 | 11.7 | 98.1 | 94.4 | 29.3 |

PPV, positive predictive value; NPV, negative predictive value

94.4%), a diagnosis of focal onset seizure is highly likely, and clinicians may consider initiating appropriate ASM for treatment of focal onset seizures while awaiting subsequent EEG and/or neuroimaging assessments.

*Clinical implications*

Classification of the seizure type is one of the fundamental steps in ASM selection for epilepsy patients. The current guideline recommended carbamazepine, levetiracetam, phenytoin or zonisamide for adults with focal onset seizures based on level A evidence.[8] Meanwhile, there was only level C evidence for ASM choices in adults with generalised onset tonic-clonic seizures.[8] Therefore, patients with focal seizures could be prescribed with ASMs which were more specific for focal seizures. Meanwhile, patients with generalised or undetermined onset seizures were often prescribed sodium valproate. Early identification of focal onset seizures also allows clinicians to pursue investigations such as MRI brain to identify potential structural lesions.

In conclusion, we present here a simple and rapid focal seizure screening tool was established with high specificity and PPV.

## ACKNOWLEDGEMENT

We would like to acknowledge the contribution of the medical laboratory technologists in the neurology laboratory, University of Malaya Medical Centre in data collection.

## DISCLOSURE

Financial support: None

Conflict of interest: None

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**Seizures (Fits) Questionnaire** **RN: _____**

I am _____, a Consultant Neurologist specializes in Epilepsy and Seizures. You are referred to have a test called electroencephalogram (EEG), which is useful to identify abnormal brain activity. I am going to interpret and report your test after it has been done. This questionnaire is helpful to me when interpreting your test.

Do you have any event(s) that your doctor thought it could be a seizure or a fit? If your answer is yes, please proceed to the following. Try your best to answer the questions, but it is alright if you are not sure. You are encouraged to ask whoever witnessed the event(s) for more details, or invite them to answer the questions together with you.

If your answer is no to the above question, please inform the staff in the counter. Your cooperation is much appreciated.

| **Background** | |
|---|---|
| 1. At what age did you first experience the event? | _____ (years) |
| **In the past** | |
| 2. Do you have blank spells or spells in which you "switch off or go off the airwaves"? □ Yes□ No □ Not sure | □ Yes □ No / Not sure |
| 3. Do you have spells in which you twitch or jerk, especially just after waking up? □ Yes□ No □ Not sure | □ Yes □ No / Not sure |
| 4. Do you have any seizures in your childhood? | □ Yes □ No / Not sure |
| 5. Is there anyone in your family with seizures or fits? | □ Yes □ No / Not sure |
| 6. Have you had any injury to the head that made you unconscious? □ Yes□ No □ Not sure | □ Yes □ No / Not sure |
| 7. Have you had any febrile episode that made you unconscious? | □ Yes □ No / Not sure |
| **Situation of the event** | |
| 8. When does the event occur? | □ Early morning (within the first two hours after wake up from sleep)<br>□ Daytime<br>□ Early sleep (before 12 midnight)<br>□ Late sleep (after 12 midnight)<br>□ Throughout the days / no specific timing |
| **At the start of the event** | |
| 9. Do you have any warning before the events occur? | □ Yes □ No / Not sure |
| 10. Do you experience dizziness? | □ Yes □ No / Not sure |
| 11. Do you experience blurred vision? | □ Yes □ No / Not sure |
| 12. Do you experience palpitations or a pounding heart? | □ Yes □ No / Not sure |
| **During the event** | |
| 13. Do you "go blank" or lose awareness of your surroundings during the event? | □ Yes □ No / Not sure |

*Seizure Score Questionnaire V2.0 designed on 03.07.2013*

| | |
|---|---|
| 14. Do you experience a feeling of being in a dream or in an unusually strange or familiar place? □ Yes□ No □ Not sure | □ Yes □ No / Not sure |
| 15. Do you experience intense fear? | □ Yes □ No / Not sure |
| 16. Do you see or hear things that aren't real? | □ Yes □ No / Not sure |
| 17. Do you experience any unusual smells or tastes? | □ Yes □ No / Not sure |
| 18. Do you notice any pins and needles, electric shocks, tingling, or other changes in sensation? | □ Yes □ No / Not sure |
| 19. Do objects or sounds in the room appear distorted or altered? For example, do sounds seem nearer or farther away or objects seem shrunken or magnified? | □ Yes □ No / Not sure |
| 20. Do you experience a funny feeling in your tummy? | □ Yes □ No / Not sure |
| 21. What happened to your eyes? | □ Closed<br>□ Eyes roll back<br>□ Eyes look to the left<br>□ Eyes look to the right<br>□ Not sure |
| 22. Does the head turn in a particular direction? | □ Yes □ No / Not sure |
| 23. Are the arms held stiff in a particular position? | □ No<br>□ Yes. Both arms are held stiffed<br>□ Yes. Only one arm is held stiffed<br>□ Not sure |
| 24. Does breathing stop or does the subject go blue? | □ Yes □ No / Not sure |
| 25. Do any jerking or twitching movements of the face, arm, or leg occur during the event? | □ No / Not sure<br>□ Jerking or twitching only in one side of the body<br>□ Jerking or twitching in both sides of the body |
| 26. Do the eyelids twitch or is there repeated blinking? | □ Yes □ No / Not sure |
| 27. Do any of the following things occur: smacking of the lips, licking of the lips, chewing, swallowing, or laughing? | □ Yes □ No / Not sure |
| 28. Do any of the following things occur: picking at or fiddling with things, walking or making stepping or bicycling movements? | □ Yes □ No / Not sure |
| 29. Do you speak during the event? | □ Yes □ No / Not sure |
| 30. Do you shout during the event? | □ Yes □ No / Not sure |
| 31. Do you ever bite your tongue? | □ Yes □ No / Not sure |
| 32. Do you ever wet yourself? | □ Yes □ No / Not sure |
| **After the event** | |
| 33. Are you confused or drowsy? | □ No<br>□ Yes. Only for a few minutes<br>□ Yes. 10 minutes or more<br>□ Not sure |

*Seizure Score Questionnaire V2.0 designed on 03.07.2013*

Thank you for your time and cooperation. Your answers will help your doctor to understand you better. Please pass this form to your treating doctor.