COMMENTARY: ILAE DEFINITION OF EPILEPSY

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This article provides added overview of the process used by the International League Against Epilepsy (ILAE) in the revised operational clinical definition of epilepsy.

The definitions process began >10 years ago, when the ILAE Executive Committee under the leadership of Jerome Engel, Jr., formed the *Definitions of Epilepsy* committee. After multiple meetings and a dozen drafts of a manuscript, the committee published in 2005[1] a conceptual definition of epilepsy with two points at variance with the traditional "two unprovoked seizures" definition. The first was that epilepsy could be considered to exist after one unprovoked seizure, provided there was an enduring predisposition for another. The second concept was to incorporate psychobiologic and social consequences of epilepsy into the definition. The committee did not provide specific meaning of the phrase "enduring predisposition," and so it remained a concept. Nevertheless, the conceptual definition generated controversy.

In 2012, Solomon Moshe, and the incoming ILAE president, Emilio Perucca, reconstituted a *Definitions Task Force* with 19 members, including three current or past ILAE presidents, a current and prior editor of *Epilepsia*, several current and past presidents of national societies, members with clinical and epidemiologic expertise, representatives of the resource-poor world, and representatives of the International Bureau for Epilepsy. The Task Force included individuals with epilepsy. The immediate charge was to clarify and make operational, that is, practical and usable, the definition conceptualized in 2005. The Task Force met in person and communicated by way of hundreds of emails. Points were debated, and ultimately 22 drafts of a manuscript were reviewed by the coauthors.

The presubmission draft of the manuscript was posted on the ILAE website with an invitation for the epilepsy public to provide comments. A total of 313 individuals did so, many with great thoughtfulness and detailed suggestions and criticisms. A few of the comments were multi-paged single-spaced essays. The signed comments can be found at http://www.ilae.org/Visitors/Centre/Definition.cfm. Input was provided from individuals with epilepsy, doctors, researchers, and also official statements from groups or societies, including the following: The German Society for Epileptology, the Brazilian League Against Epilepsy, the China Association Against Epilepsy, Andrews-Reiter Epilepsy Research Program, the National Association of Epilepsy Centers, the Epilepsy Coalition of New York State, and the Norwegian Institute of Public Health. Overall, there were 174 positive comments (56%), 64 negative comments (20%), and 75 neutral comments (24%). Comments with at least two criticisms were counted as being negative, even when accompanied by effusive praise. The authors categorized the public comments and substantially altered the manuscript and definition based on prevailing themes.

A frequent question was, "Why do this"? The default definition of epilepsy as two or more unprovoked seizures at least 24 h apart, although never officially adopted by the ILAE, is a simple, easily applicable, and consistent definition. However, as discussed in the 2014 publication,[2] clinicians consider epilepsy to exist in certain circumstances after one seizure. If the risk for subsequent seizures is known to be as high in one person as for another who meets the traditional definition, why not consider both to have epilepsy? Another motivational force for modifying the definition was discomfort with the notion that epilepsy is forever. A decision was made to develop a revised operational clinical definition, but not to invalidate the traditional definition, which could be operationally applied by epidemiologists or other groups desiring methodological consistency with past studies.

Among those posting comments, 28% did not like using a point cutoff, originally a 75% risk for a second seizure, to define epilepsy. We therefore switched to a confidence interval denoting the risk range of a third seizure after two unprovoked seizures, which is about 60–90%. We clarified that the practitioner does not carry a burden of knowing the risk for a second seizure. Diagnosing someone as having epilepsy after one unprovoked seizure with high risk for another is on an "opt-in" basis, when the risk is known and the clinician is comfortable making a diagnosis. When a cli-

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nician is faced with unclear or unknown recurrence risks, the old definition applies.

Epilepsy should be called a disorder according to the 23% who spontaneously so commented. The ILAE Executive Committee decided in favor of calling epilepsy a disease, and the Task Force did not further debate the issue.

A total of 8% of the respondents mentioned ambiguities regarding provoked versus unprovoked seizures. Although the boundaries often blur, eliminating this concept would have caused substantial confusion. The Task Force therefore retained the concept of provoked and unprovoked seizures and added clarifying language. Some responders liked the idea of defining a condition called "probable epilepsy," and others did not. The Task Force did not define probable epilepsy, but another group might do so in the future.

Little controversy arose over including reflex epilepsies in the definition of epilepsy, although such seizures are provoked. Most members of the Task Force thought all along that reflex epilepsy was epilepsy, and the definition simply made that explicit. Some operational definitions of epilepsy have placed a 5-year window on time to have the second seizure. Doing so has obvious practical value in allowing a discrete period of data collection. Nevertheless, the Task Force could not find good evidence for setting any particular time interval as an outer limit for a second unprovoked seizure. Therefore, with some discomfort, we considered someone to have epilepsy with any two lifetime unprovoked seizures. An exception is for two seizures known to have different etiologies.

Most respondents liked the idea of defining a way to "outgrow" epilepsy. This is self-evident when a child has outgrown the age of a time-limited syndrome, such as benign epilepsy with centrotemporal spikes. A total of 6% of respondents argued that people should no longer have epilepsy after 5 years of being seizure-free. Because several percent of such individuals relapse, the Task Force extended the required time to 10 years seizure-free. Few relapse after achieving those milestones. The public commenters did not agree on using the terms "cure," "remission," or "no longer present" to define the state of outgrowing seizures. The Task Force settled on calling the epilepsy "resolved" after outgrowing an age-limited syndrome or being seizure free for 10 years, with the last 5 years off antiseizure medications.

After the manuscript was revised based on the public comments, a new task force was empaneled to evaluate whether the revision adequately reflected the public view. The new task force agreed, with a few provisos, that the comments had been addressed. The manuscript was submitted to *Epilepsia* (with the author-editor recusing himself from the review process). Thirty-three anonymous comments were received from five reviewers, and the article was again revised in accord with those suggestions. After acceptance of the manuscript by *Epilepsia*, the ILAE Executive Committee voted to make the definition a position of the ILAE.

Few manuscripts in the epilepsy literature have undergone such an extensive review and revision process. Obtaining consensus from 19 strongly opinionated authors was itself a challenge, and then four additional layers of commentary and revision ensued: (1) from the public; (2) from the comment review Task Force; (3) from *Epilepsia*; and (4) by the ILAE Executive Committee. The resulting definition and publication were much strengthened by this process and better aligned with the way clinicians think about epilepsy. Codifying that thinking is the purpose of a definition. As new information and experience accumulate, the way clinicians and researchers view the term "epilepsy" will evolve, and another revision of the definition may be required—it is hoped not any time soon.

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References

1. Fisher RS, van Emde Boas W, Blume W, et al. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). *Epilepsia* 2005;46:470–472.
2. Fisher RS, Acevedo C, Arzimanoglou A, et al. A practical clinical definition of epilepsy. *Epilepsia* 2014;55:475–482.