AMERICAN EPILEPSY SOCIETY

Walter J Koroshetz MD,
Director, National Institute of Neurological Disorders and Stroke

Re: NINDS Request for Information (RFI) Developing an Online Educational Resource for Training in the Principles of Rigorous Research
Notice Number: NOT-NS-20-062

July 31, 2020

Dear Dr. Koroshetz and colleagues,

The American Epilepsy Society appreciates the opportunity to comment on best practices and innovation for education in the principles of rigorous research, and the promotion of rigorous research practices.

As an education provider, we call out the infrastructure to engage diverse stakeholders as one strategy to consider how to maximize research education. We would be happy to comment further should the NINDS have additional specific questions.

Sincerely,

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American Epilepsy Society (AES)
Written Comments to
NINDS Request for Information:
Developing an Online Educational Resource for
Training in the Principles of Rigorous Research
Notice Number: NOT-NS-20-062

AES Written Comments were reviewed and approved by the AES Research & Training Council and the AES Executive Committee in July 2020. Comments were authored by the NINDS RFI Workgroup, Education on Rigor, with expertise spanning education and basic, translational, and clinical research: Barbara Jobst MD (Chair), Ravindra Arya MD DM, E. Martina Bebin MD MPA, Shilpa Kadam PhD, David Loring PhD, and Jamie Maguire, PhD.

Submitted on July 31, 2020

Question 1:
What are the most important principles of rigorous research for all scientists to understand?

Our comments reflect the collective expertise and viewpoint of the AES, whose 4500 members are clinical care providers and scientists who share a commitment to improved outcomes for children and adults with epilepsy, seizures, and related disorders.

All components of rigorous research drive towards a shared key goal of reproducibility. Principles of rigorous research span every step of research from experimental design and study execution to analysis and publication. The education on such principles should be entwined with education on research ethics.

While some principles of research rigor are universal, others are specific to a given field of research and must therefore rely upon the experts within that field to inform and develop education on rigor. For example, in epilepsy research, new models of genetic or acquired epilepsies continue to emerge, often by PIs who may be excellent scientists but lack training in the requirements of rigorous characterization of an epilepsy model. Epileptiform events might be "demonstrated" with only a sample EEG, omitting the resource-intensive yet essential steps of EEG monitoring protocols with use of blinded scoring, quantification of frequency, diurnal distribution, or natural history, let alone universal standards for rigor such as appropriate sample sizes, consideration of relevant biological variables, appropriate matched controls.

Universal principles in research rigor can be often found in courses on experimental design and philosophy of science, although such courses are not always accessible or well-advertised at institutions. Courses on statistics are more commonly accessible but often fail to comprehensively cover key principles such as sources of bias and confounding, the meaning of null hypothesis testing and use of probability levels (e.g., $p<.01$), as well as effect sizes, confidence intervals, clinical meaningfulness, chance findings and the importance of replication. Important principles are often omitted from formal course work. The influence of base rates regarding diagnostic predicative accuracy is typically poorly understood by trainees and junior investigators.

The methods of systematic reviews could be a valuable teaching tool even for those who will not perform the reviews themselves, as it reinforces the consideration of all available

research rather than selective narrative reviews. It also emphasizes replicability of findings, and at least indirectly, embraces the "file Drawer" problem.

Important principles are often omitted from formal course work. The influence of base rates regarding diagnostic predicative accuracy is typically poorly understood by trainees and junior investigators. Principles on data sharing and data transparency are essential for reproducibility. Checklists from the Equator Network can aid in their implementation. Distinctions should be reinforced between hypothesis driven versus exploratory research to generate hypotheses. With pre-defined hypothesis – maximum details for sample size estimation, methods, data analyses and transparency for interpretations should be provided and subsequently reported with the appropriate EQUATOR checklist.

While an understanding of key principles is important, changes to infrastructure and incentives could help empower researchers to transform such principles from aspirational goals to consistent practice. Below, we suggest some potential strategies.

Preregistration of research plans could be more heavily adopted to better enable peer-review of research methodology prior to study execution, increase the likelihood of publishing "null" results, and underscore the importance of replication.

To assure rigor of research the review of grant proposals and manuscripts for publication should be shifted to prioritize reproducibility and rigor. Despite increasing recognition of the importance of replication, grant proposals are evaluated almost exclusively upon "novelty." Proposals explicitly designed at replication are discouraged and typically triaged. Lack of novelty should not automatically be considered a study weakness. If these rigor and reproducibility are listed separately and specifically on the review template sheet, this will redirect the entire study section to not only discuss it but also focus on it themselves in their grant writing. Similar changes might be made to the publication process so that reproducible data results could be prioritized equally with non-reproduced yet novel data. A culture of publishing negative results of well conducted studies, especially clinical trials will set the culture of rigorous research.

Ultimately, primary investigators and institutional leaders must create an atmosphere to celebrate rigor at the department and research institutions, with celebration of rigorously generated null results for trainees and recognition of senior personnel who mentor in rigorous design. Such atmospheres can be fostered through financial support (e.g. the NIH and other agencies) and the creation of a "score" for rigor so that the success of a research portfolio can be more easily judged by its rigor as well as its impact factor.

Question 2:
For each career stage (undergraduates, graduates, post-docs, and faculty), what are the best teaching practices to use (i.e. how to convey information in a lasting and impactful way)?

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share a commitment to improved outcomes for children and adults with epilepsy, seizures, and related disorders.

Principles.

1) Learners may have different goals for learning principles of rigorous research at different stages of their career and at different time points. These goals may include both appraisal of research (e.g. literature review for clinical decision making) and generation of research (e.g. designing and implementing a research study to address a knowledge gap).
2) The dynamics of availability of information resources, their access, and the manner in which learners at different career stages and at different times interact with these resources, are constantly shifting.
3) The ***overarching objective*** of any educational program is to optimally match the goals of individual learners at a given time, their level of training in research methodology, and the pedagogic technique. Any such educational program should have enough resilience to accommodate constantly changing dynamics of learning as mentioned above.

Educational Resources.

A majority of the following teaching and learning resources are available in different formats such as print, online, and offline soft version. The earlier education occurs in someone's career, the more those concepts are likely to be engrained into the researcher's core principles.

Principles of rigorous research should definitely be communicated at the graduate level for preclinical research and at the resident and fellow level for clinical research. Within clinical education research relevant teaching is not always emphasized and principles of rigorous research should be integrated into resident and fellow education.

Undergraduate and medical school education (beginner level below) is very broad and should include some basic principles of rigorous research but probably do not need to go into excessive detail.

At a post-doc and faculty level there should already be awareness of the principles of rigorous research but this cohort would benefit from updated learning.

Teaching/Learning Resource	***Best Utility for Career Stage****
Textbooks	Beginner
Didactic lectures (including webinars)	Beginner to Mid-level
Live interactive sessions/Q and A	Mid-level to Advanced
Mentored sessions for study design/research proposal review	Mid-level to Advanced
Mock study sections	Mid-level to Advanced
Original articles related to research methodology (e.g. new or domain-specific statistical computational methods)	Advanced
Web based interactive e-learning	All levels
Review articles	All levels
RSS feeds, small "information nuggets"	All levels

Irrespective of the career stage, we have used the following arbitrary classification.

- ***Beginner***: Exploring interest in rigorous research.
- ***Mid-level***: Having a specific research objective, looking to critically appraise the literature, or design a research study to address that objective.
- ***Advanced***: Previous experience with successful design and implementation of rigorous research. Also includes reviewers and journal editors.

Potential Strategies to Maximize Research Education.

1) ***Infrastructure to engage all stakeholders.*** Professional societies and other 3rd party organizations can sometimes provide training resources tailor-made to the needs of a given field. For example, the American Epilepsy Society offers a portfolio of e-learning resources, including an introductory curriculum for clinical research in epilepsy and mentorship on grantsmanship. The NIH could foster the engagement of such organizations by a) offering incentives to investigators or institutions to use such resources, for example as part of the training requirements for a given grant, and b) offering funding opportunities for education development.
2) ***Defining rigorous research and the core curriculum***. Perhaps the first goal to develop an effective educational program will be to establish a core curriculum encompassing the common minimum tenets of rigorous research. These core tenets should transcend across specific domains, should be suitable for any level of learning, and include research methodology, ethics, integrity, and transparency. One possible way to develop such a curriculum could be Delphi process including all stakeholders.
3) ***Incentivize learning***. Reinforce the value of learning to trainees through financial and career incentives.
4) ***Diversity and consistency of exposure***. For any educational program to transform the rigorousness in biomedical research, it will be desirable to offer a diversity of resources to individual learners, so that they can choose the best format, depending on their specific objective, career stage, and time availability. These learning formats could include all the resources mentioned above including web based learning. Also, it will be important to ensure that these diverse resources emphasize the same core principles of rigorous research.
5) ***Opportunities for teaching and learning research methodology***. The teaching and learning of principles and methodology of rigorous research should not be restricted to sessions solely intended for that purpose. Instead, any clinical or academic opportunity can be harnessed for the impetus on rigorous research. In addition to dedicated sessions, discussions in clinic, at the bedside, and in case conferences could be utilized to illustrate rigorous research-oriented thought process.
6) ***Repurposing journal clubs***. Journal clubs are essential components of residency and fellowship academics, which are also attended by faculty members. They can be utilized to emphasize good research methodology by enhancing the participation of statisticians or research methodology experts. In addition to the subjective content of the journal articles being reviewed, it is highly advantageous to spend time on critically analyzing the research methods used by the investigators, learning about the statistical or other quantitative techniques used therein, and potentially discussing avenues for improvement in the same.

7) ***Panels for protocol and grant reviews***. Given the variability in expectations, resources, and sophistication in resident and fellow research, trainees and early career investigators may benefit from workshops to discuss their research proposals with peers and experienced researches.
8) ***Sustained individual extra-mural mentorship***. This is exemplified by the AES EPIPORT (Epilepsy Patient Oriented Research Training) program, where the trainee sends in a draft proposal and is matched with an external mentor, who then provides ongoing guidance for developing the funding proposal and its proposed experimental design.
9) ***Creation of a statistical toolkit***. Clinical investigators, particularly those early in their training and career have variable proficiency in statistical methods. For those with limited statistical background, it may be valuable to have an online statistical resource to perform power estimation and some straight-forward statistical tests. Many such online tools are available, and may be adopted, or a new tool can be created for this purpose. Funding for statistical consultants is also highly effective.
10) ***Formal training in research methodology during residency and fellowship***. Including even a small formal component of research methodology training during earlier states of professional career, can inculcate a culture of rigor and critical thinking to adapt and create scientific evidence for clinical practice. Incentives and infrastructure are key, for example to include a research methodology component in institutional assessments and board exams. Research training should be customizable to meet the needs of different programs. For example, the needs of a neuroscience graduate student differ from that of a child neurology resident motivated to critically evaluate and integrate research into her practice, or a neuro-radiology resident with computer science background who wants to pursue image-processing research.

Practices with evidence for success in teaching research methodology
1) Focus on real clinical and scientific applications. 2) Focus on learners' actual needs. 3) Balance active and passive learning. 4) Connect new knowledge to old (what the learners already know) 5) Match, or take advantage of, the circumstances including the clinical setting and time 6) Balance preparedness with opportunism 7) Build learners' abilities for future self-learning Modified from: Straus, S. E., Glasziou, P., Richardson, W. S., & Haynes, R. B. (2018). Evidence-Based Medicine E-Book: How to Practice and Teach EBM. Elsevier Health Sciences. Pinsky, L. E., Monson, D., & Irby, D. M. (1998). How excellent teachers are made: reflecting on success to improve teaching. *Adv Health Sci Educ.*, 3(3), 207-215.

Question 3:
For each career stage, what is the ideal delivery structure and how often should these principles be reinforced?

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share a commitment to improved outcomes for children and adults with epilepsy, seizures, and related disorders.

Training in the Principles of Rigorous Research is essential for maintaining scientific integrity and public trust in the scientific community. Efforts to develop an online educational resource will ensure standardization of training and compliance. We have developed recommendations to ensure effective training throughout the scientific community. Training in the Responsible Conduct of Research (RCR) is an excellent example of essential training which has been effectively administered throughout the scientific community. We recommend following a similar training structure for Training in the Principles of Rigorous Research:

1. Require that Training in the Principles of Rigorous Research, including fundamentals of study design, is required for predoctoral and postdoctoral NIH National Research Service Award (NRSA) Fellowship applications.
2. Require that all trainees supported by NIH funds receive training in the Principles of Rigorous Research, refreshed every four years, and that such training is addressed in progress reports for NIH grants.
3. Propose that the ACGME incorporate training in research and research rigor, including fundamentals of study design, as a required component of accredited clinical fellowships.
4. Add a section in NIH grants for the PI to outline issues specific to their grant that relate to the broader concerns of rigor, then require that the PI discuss those issues with the individuals working on the grant.

This periodic training can be reinforced by helping investigators access the training that they need at the time that they need it for their own goals. For example, an online library of concise training modules, with a robust searchable interface, could allow investigators to access refreshers on a given topic at the time that they need it, for example when designing or analyzing a given experiment. This concept of a toolkit is outlined further in our response to Question 4 (below).

Question 4:
If delivered as an online resource, what is the most effective balance between different educational media (e.g. text, video, interactive activities)?

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Training in the Principles of Rigorous Research is essential for maintaining scientific integrity and public trust in the scientific community. Efforts to develop an online educational resource will ensure standardization of training and compliance. The platform for delivery of this information is critical. A completely online didactic format may have the appearance of a "checkbox" training rather than actually fulfilling the goal to educate the scientific community in the Principles of Rigorous Research. We have developed recommendations to

ensure effective training throughout the scientific community. We recommend a multi-media approach to Training in the Principles of Rigorous Research as outlined below:

1. Develop an online Toolkit for Training in the Principles of Rigorous Research, including fundamentals of study design. Compiling essential tools for planning and executing rigorous research in a single approved location would be a valuable practical asset The toolkit could incorporate power analysis calculators, statistical recommendations, technical and biological replicates, and recommendations for blinding and counterbalancing proposed experiments as well as providing educational feedback about the specific recommendations. The toolkit might also enable access to field-specific resources, such as the preclinical common data elements developed by the ILAE/AES Joint Translational Task Force to foster reproducibility in translational preclinical epilepsy research. Although many online tools are available, their validity has not been independently established and have not been compiled into a comprehensive resource. Further, as part of this toolkit, there could be feature where trainees could be presented various basic or clinical research vignettes associated with each topic module and asked to complete educational "quizzes" with feedback to test and reinforce their understanding of important research concepts.
2. Interactive online education is ideal to ensure understanding of the trainees. Short video modules (10-15 minute max) with high production quality would be an effective strategy, incorporating cartoons or infographics rather than a long video of one person talking,
3. Interactive research studies would also be effective. The video could be designed to be interactive such that the trainee could make decisions on their course of action and then go through training regarding the potential consequences of those choices. This interactive video-based online training would help reinforce the relevance of the training. Example of poorly designed or poorly analyzed research should also be presented with discussion of incorrect conclusions and study inference based upon faulty study design.
4. Recommendations for standard operating procedures and best practices for labs to reinforce best practices in the lab.