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LETTER TO THE EDITOR

Translational Stroke Research Guideline Projections: The 20/20 Standards

Paul A. Lapchak[1] · **John H. Zhang**[2]

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Dear Editor:

The future of innovative and effective preclinical and translational drug development for neurodegenerative disease, if conducted in an academic environment, will require a series of changes to funding, methodologies, and data management. For the changes to be executed and established in the research community, it would be beneficial to stroke victims if the research community could establish an aggressive, but reasonable timeline. Even with new "stroke prevention methods", the actual stroke incidence (795,000 in 2009 maintained at 795,000 in 2016) has not changed over the last 7 years [1–4], so there is still an urgent need for new therapy development.

The recent *Translational Stroke Research* special issue entitled *Challenges and Controversies* addressed to some extent the hurdles that have to be overcome to develop a stroke therapy [5] including the need for appropriate control groups [5], utilization of the best choice rodent strain, since there are physiological differences that are inherent to different stains [6], understanding of stroke variability and heterogeneity [7], need for gender analysis [8], inclusion of aged animals, and possibly other comorbidities [9], study design to determine clinically relevant therapeutic windows [10], and application of combination therapies [11], which is extremely important considering the growing use of endovascular procedures [12, 13]. Most of the special issue articles mentioned and cited stroke therapy academic industry roundtable (STAIR) and RIGOR guidelines [14–18], but they did not delve into detailed requirements for the published guidelines.

The 20/20 standards described here have multiple purposes. First, to propose that research methodologies can be further refined to include good laboratory practices (GLP) as previously reviewed in detail [19, 20]. There are two levels of GLP that should be adhered to while conducting translational research: first, there are recognized GLP standards directly related to the research laboratory environment, but the standardization of a laboratory can be costly. In the long term, a GLP laboratory will be cost-effective, but in the near-term, this requires a substantial investment by funding agencies and oversight by principal investigators and academic institutes. The basic GLP laboratory will be required to have readily available extensive documentation relating to facilities, protocols, assay standardization, and equipment. For example, a standard laboratory should have all equipment calibrated annually. While this may seem unimportant, the simple example of annual calibration of anesthesia vaporizers needs to be emphasized, since altering the delivery of anesthetics (i.e., isoflurane) in a rodent can be directly related to the neuroprotective effects of anesthetics [21]. There is literature describing dose-dependent, preconditioning effects of anesthetics when applied prior to a surgical procedure [22]. Also, under certain circumstances, high-dose (4–5%) isoflurane during surgery in rodents can prevent ischemia, at least to some extent (personal communications).

Macleod et al. [19] introduced the *Good laboratory practice* (*GLP*) to prevent the introduction of research bias; the document was a predecessor of the 2010 Animals in Research: Reporting In Vivo Experiments (ARRIVE)

✉ Paul A. Lapchak
Paul.Lapchak@cshs.org

John H. Zhang
johnzhang3910@yahoo.com

[1] Department of Neurology & Neurosurgery, Cedars-Sinai Medical Center, Advanced Health Sciences Pavilion, Suite 8318, 127 S. San Vicente Blvd, Los Angeles, CA 90048, USA

[2] Center for Neuroscience Research, Loma Linda University School of Medicine, 11175 Campus St, Loma Linda, CA 92350, USA

[23–30] and subsequent 2012 RIGOR guidelines [16–18]. While the ARRIVE guidelines have been published to promote transparency in publication, this also requires parallel transparency in research conduct. The recent RIGOR guidelines did not incorporate STAIR or ARRIVE guidelines, because RIGOR was a call for research transparency and not specific translational study design. In fact, a comprehensive set of guidelines that can be applied by all translational stroke researchers has not been discussed or adopted by the research community.

The timely editorial by Marbacher [31] in *Translational Stroke Research* is on the right track; it was educational and quite informative since the author provided a table with a list of links to guidelines. As the author indicated in the commentary, many researchers still do not think that applying guidelines is a priority in the translational stroke field. The original 1999 STAIR and 2009 STAIR [14, 15], 2010 ARRIVE [23–30], and 2012 RIGOR guidelines [16–18] are being applied to some translational research studies, and drug development opportunities, but there is still low compliance. Needless to say, there is a great deal of confusion regarding what is required of stroke researchers so that they can conduct quality research, but it remains clear that improvement in the transparency of scientific research is required to focus on the

Table 1 Comparison of current research guidelines

Process	STAIR	ARRIVE	GLP	RIGOR	2017 data standards	VOW	20/20 projected standards
References	[14, 15]	[23–30]	[19]	[16–18]	[20]	[32, 33]	
Acute outcome	X						X
Allocation concealment	X		X	X			X
Animal (strain and source)		X	X				X
Archived data					X		X
Assay/model rationale/validation				X	X		X
Blinding (all aspects of study)	X		X	X			X
Combination studies (i.e., tPA)			X				X
Comorbidity—age-adjusted dosing-dose scaling	X					X	X
Comorbidity—aging	X					X	X
Comorbidity—diabetes	X					X	X
Comorbidity—hypertension	X					X	X
Conflict of interest statement	X			X			X
Data audits					X	X	X
Data publication (−ve/+ve/neutral)				X		X	X
Dose response curve	X	X					X
Equipment calibrated					X		X
Ethical/humane		X					X
Funding source			X				X
Gender analysis	X					X	X
Good laboratory practice				X	X	X	X
Inclusion/exclusion criteria	X		X	X			X
Long-term outcome	X					X	X
Multiple laboratories	X					X	X
Multiple species	X	X					X
Physiological monitoring	X	X					X
Power analysis (sample size calculation)	X		X	X		X	X
Protocol archived					X		X
Randomization	X		X	X		X	X
Reproducibility			X	X		X	X
Route of exposure (oral, sc, iv)	X						X
Statistical analysis method			X	X		X	X
Therapeutic window	X					X	X
Toxicity	X						X

VOW visions and opportunities workshop (NINDS 2016)

discovery and drug development process so that a treatment can be provided to patients.

In this letter, we will briefly focus on stroke as an indication for new therapy development, the primary focus of this journal, and both authors have some familiarity with the topic. In Table 1, we provide a comprehensive list of *processes* or recommendations mined from the literature publications of focused guidelines published to date. The ARRIVE guidelines have been treated as scientific experimentation guidelines, rather than as guidelines for publication of research data. The *mandatory* requirements have continued to evolve since the original STAIR criteria were published, because the field is still struggling and striving toward the development and approval of a neuroprotective or cytoprotective agent. There are few commonalities between the guidelines that should be addressed for the initial phase I development phase, and they are as follows, in order of importance:

Phases I and II

1) Standard RIGOR: blinding, randomization, and adequate statistical analysis: every study should be conducted with RIGOR and transparency.
2) Good laboratory practice: while this is extremely important, but this can be cost prohibitive unless funding agencies support the practices.
3) Archived: auditable data: this practice will increase research transparency.

Phase II

4) Gender analysis: this is recommended for phase 2 studies to incorporate age.
5) Inclusion of aged animals: this is cost prohibitive under the current funding structure. Aged animals should only be included during phase 2 studies once reproducible proof of concept data has been obtained in young animals.
6) Reproducibility in multiple laboratories: this is recommended for phase 2 studies. Patentability of compounds may preclude testing in multiple laboratories during phase 1.
7) Efficacy validation in second species: a stringent test should be done in a non-rodent species.

Phase III: see [34]

As evident in Table 1, there are too many criteria for a standard research laboratory to incorporate into programs at this time because of the low levels of funding on which most laboratories are subsisting. Thus, we propose the 20/20 projected standards for the stroke field as indicated in the table. Perhaps by 2020, and we are all hopeful that funding levels will have caught up with the urgency and need for a cytoprotective drug for stroke, there will be a greater appreciation by funding agencies of the costs associated with all aspects of drug development in academic laboratories [35]. Clearly, a paradigm shift is necessary to promote critical translational research and provide sufficient seed and development funds to researchers based upon limited preliminary and/or proof of concept data to avoid abandoning promising new drug development opportunities.

Sincerely,

Paul A. Lapchak, Ph.D., FAHA

John H. Zhang, M.D., Ph.D, FAHA

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Compliance with Ethical Standards

Conflict of Interest PAL is Editor-in-Chief, Journal of Neurology & Neurophysiology and Associate Editor, Translational Stroke Research; JHZ is Editor-in-Chief, Translational Stroke Research Editor-in-Chief, Medical Gas Research.

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