Recommendations and Practices to Optimize Stroke Therapy Developing Effective Translational Research Programs

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On June 20 and 21, 2012, a National Institute of Neurological Disorders and Stroke-sponsored workshop on “Optimizing the Predictive Value of Preclinical Research” was held in Washington, DC. The primary objective of the workshop was to review deficiencies in preclinical and translational research and provide recommendations or guidelines to improve the rigor of preclinical research. The following is based on open discussions held at the meeting and panel recommendations for the application of basic principles of experimental design and reporting transparency that are currently standard of practice for stroke clinical trials. This article, which includes author interpretations of discussions, emphasizes the need for good laboratory practices, transparent scientific reporting, and the use of translational research models with clinically relevant end points to develop new strategies to treat stroke.

Need to Treat Stroke

There is a critical medical need for new therapeutic strategies to treat acute ischemic stroke and hemorrhagic stroke to reduce mortality and improve the quality of life for stroke victims. Current US statistics indicate that stroke is the fourth leading cause of death and the leading cause of adult disability in the United States, with upward of 795,000 victims annually who suffer a new or recurrent stroke, despite improved diet, and control of diabetes mellitus, hypertension, and hypercholesterolemia. Currently, the only Food and Drug Administration-approved treatment for stroke is the thrombolytic, tissue plasminogen activator (tPA) if administered within 3 hours of a stroke. Recently, the therapeutic window for tPA has been increased and shown to be beneficial if patients are treated within 4.5 hours of an ischemic stroke. However, the Food and Drug Administration (FDA) has not yet approved the extension of the time window >3 hours. Although thrombolysis is now widely accepted as a standard of care for acute ischemic stroke, only a minority (6%) of acute ischemic stroke patients are treated with tPA in the United States. A recent cost-effectiveness survey showed that there was an incremental benefit, measurable in terms of quality-adjusted life-years, to the patient administered tPA compared with patients with no treatment, in the acute ischemic stroke patient population with National Institutes of Health Stroke Scale (NIHSS) Scores of 0 to 19. However, the analysis showed reduced benefit of tPA in patients with a National Institutes of Health Stroke Scale score >19, and there was no benefit in diabetic patients or patients with atrial fibrillation.

Stroke Research Design and Reporting: Are There Deficiencies?

A thorough review of preclinical research conducted under the Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies (CAMARADES) projects has revealed an important trend in preclinical research data. As documented in a presentation by Dr Malcolm Macleod, there are data to support the following conclusions: (1) the measured effect in a study, primarily improvement was larger when done by investigators with a study that was not randomized; (2) the measured effect was larger in studies done by investigators when there was no blinded assessment; (3) only 3% of published studies included power analysis calculations; and (4) a significant amount of unpublished negative or neutral data results in an overestimation of efficacy because the majority of published data are positive.

Central to these points are the observation that in stroke research, only 36% of published studies reported randomization and only 29% of published studies were blinded. The absence of randomization and blinding introduces a bias in the studies, especially, when the investigator knows the order of groups and the specific treatment(s) given to the group. The absence of power analysis calculations has a couple of implications. First, it would suggest that the studies may not include sufficient numbers of animals for statistical significance on the primary end point to be measured (underpowered). Second, in studies with multiple end points, analysis of ≥1 end points may be underpowered. This would not allow the investigator to effectively correlate data between multiple end points. Finally, as has been reported for NXY-059, the majority of NXY-059 data published in the literature were overwhelmingly positive, and there was investigator and publication bias even though 40% of studies reported randomization, 53% reported surgeon, and 67% reported assessment blinding. Part of the bias present in studies may be because of funding restrictions and limitations to a specific laboratory requiring a single investigator to conduct surgery, administer drugs, and even complete final study assessment. Each translational study will

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need to incorporate a minimum of 2 investigators to remove study bias.

**Recommendations for Study Design and Reporting**

On the basis of presentations during the workshop, there were few recurring recommendations for advancement of translational research. It was suggested that the recommendation be incorporated in translational grant applications and scientific publications, independent of the source of funding. Clearly, standardization of studies conducted worldwide will ensure reproducibility and, hopefully, translation in positive clinical trials.

The first focus is experimental design. Although there is a significant debate regarding animal models that should be used for translational research,\(^{16-19}\) patient population data show that ischemic stroke is heterogeneous with some patients presenting with small lacunar strokes and cardioembolic strokes with others.\(^{20-23}\) Nevertheless, the investigator must clearly define the rationale for the selected models and end points to be studied. The study should be properly powered based on historical data, which will allow for power analysis calculations to include adequate control groups. If there are multiple end points to be measured, the investigator should indicate how the study was powered and for what specific end point. With proper control and treatment groups, choice of statistical analysis methods used in the analysis and interpretation of results will become important.

The second important consideration is minimizing study bias. The primary method recommended to minimize investigator bias is complete study randomization, allocation, and concealment of the randomization key until completion of all study analyses. Because CAMARADES showed correlative data for better efficacy when the investigative team was neither blinded nor the study randomized, the importance of adequate randomization and blinding is essential. As alluded previously, the study will require at least 1 member of the experimental team to remain naive to the study design, and the investigator charged with drug administration cannot be the person to randomize and blind the study. Moreover, to maintain blinding, the investigator responsible for end point determination (ie, behavioral analysis or infarct volume, as examples) should be naive to the experimental groups and order/randomization of drug administration. A recommendation is made to use websites, such as http://randomizer.org/ to produce randomization tables for all groups to be included in the study once power analysis for the number of animals per experiment (ie, n or N) is established.

Once the study has been conducted and data have been accumulated, results must be interpreted and addressed. Because of a bias for overestimating efficacy in many pharmacological studies, it is important to report all results derived from a study, including both negative and positive findings. Historically, it has been difficult to publish negative research findings,\(^{24,25}\) that is no longer the case. Investigators should endeavor to report all data including data missing because of attrition or exclusion. For translational research program, independent validation and replication of studies will be an important factor when deciding whether or not to further develop a treatment strategy. As recently recommended by stroke therapy academic industry roundtable, the investigator should incorporate studies to replicate findings in a second external laboratory and if possible, in a second species.\(^{26-28}\) An alternative strategy is the establishment of an international multicenter translational animal trial network\(^{29}\) to advance potential therapy candidates to clinical trial. This strategy will ensure robust reproducible results to validate the target and drug efficacy profile. Standard good laboratory practices should be followed for all pharmacological studies using standard dose-response analysis, appropriate therapeutic window analysis, and reproducibility studies at all sites should also be conducted in a blinded and randomized manner.

**Future Translational Stroke Research**

The development of new stroke treatments has slowed considerably because few prominent clinical trials were halted owing to significant adverse events or reported lack of efficacy after promising results in initial trials\(^{30-32}\) and preclinical research that satisfied accepted criteria by the stroke therapy academic industry roundtable committee. Because stroke therapy academic industry roundtable criteria have been insufficient to ensure translation of preclinical research in positive clinical trials, the following recommendations are made to investigators so that translational research can be conducted using good laboratory practices. The RIGOR guidelines discussed above, and in detail by Landis et al,\(^{33}\) suggest that inclusion of method of blinding, study group randomization, complete power analysis, and statistical analysis be incorporated in study design. A conflict of interest statement is required for all study investigators to include sources of funding for the study, collaborations with the pharmaceutical or biotechnology industry, scientific or clinical advisory boards, financial interest in the industry broadly related to current work.

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**References**


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