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Scientific Rigor Recommendations for Optimizing the Clinical Applicability of Translational Research

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Abstract

The approval of new therapies to treat neurodegenerative disease conditions by the Food and Drug administration (FDA) has been hindered by many failed clinical trials, which were based upon "significant" efficacy in preclinical or translational studies. Additional problems during drug development related to significant adverse events and unforeseen toxicity have also hampered drug development. Recent reviews of preclinical data suggests that many studies have over-estimated efficacy due to poor or inadequate study design, exclusion of important data (negative or neutral) and lack of study randomization and blinding. This article describes in detail a set of recommendations to improve the quality of science being conducted in laboratories worldwide, with the goal of documenting in the peer-reviewed literature, including Journal of Neurology and Neurophysiology, the scientific basis for the continued development of specific strategies to treat neurodegenerative diseases such as Stroke, Alzheimer's disease, Huntington's disease, Parkinson's disease, Spinal cord injury, and Amyotrophic lateral sclerosis. The minimum recommendations for effective translational research include the need for model justification, study group randomization and blinding, power analysis calculations, appropriate statistical analysis of all data sets, and a conflict of interest statement by investigators. It will also be beneficial to demonstrate reproducible efficacy in multiple species and in studies done by independent laboratories.

Keywords: Translational; Brain; Neurodegeneration; Clinical trial; NIHSS; STAIR; STEPS; RIGOR

Introduction

Reproducible translational research may be the key to the success of new therapy development for neurological diseases such as Acute ischemic stroke (AIS) and Hemorrhagic stroke [1,2], Alzheimer's disease (AD) [3], Amyotrophic lateral sclerosis (ALS) [4,5], Huntington's disease (HD) [6], Parkinson's disease (PD) [7,8] and Spinal cord injury (SCI) [9]. Together, the 7 neurodegenerative conditions are estimated to affect a minimum of 1,224,150 new patient cases annually in the USA. Even though health care costs are continuously escalating, a conservative cost estimate using values over the last decade suggests that the annual financial burden to society for hospitalization, treatment, rehabilitation and nursing home care for AIS is $162-200 billion [1,2,10], $210 billion for AD [3], $23-25 billion for PD [11] and $8.34-9.68 billion for SCI [12]. The prevalence of every neurodegenerative disease is expected to increase at least 2-3 folds within the next 20 years.

Since there remains a critical medical need for new therapeutic strategies to treat neurodegenerative diseases, specific scientific research criteria must be established and utilized so that basic research can be transferred into positive clinical trials, which will ultimately improve the quality of life for a wide variety of patients with neurodegenerative disease. This article will emphasize that good scientific laboratory practices, transparent scientific reporting and the use of translational research models representative of the disease state, with clinically relevant endpoints, will be beneficial to systematically test and develop new treatments. New treatments will improve the quality of life for victims as well as have a strong impact to reduce the financial burden to society. It is doubtful that significant progress will be made without rigorous translational research studies using a set of internationally standardized guidelines or recommendations.

The rigors of drug development

A historical overview of modern preclinical research [13,14] citing the Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies (CAMARADES) projects provides significant insight into the basis for the lack of efficacy of drugs being developed to treat neurodegenerative disease conditions, as well as many other conditions that affect the human population during the aging process. The findings are quite disconcerting, because the majority of scientists conduct research at the highest level possible so that diseases can be treated! For example, the studies clearly show that investigators report larger measured effects, or improvement in one or more endpoints when the study was neither randomized or when endpoint assessment was not blinded. Specific to stroke research, a literature survey shows that 36% of published studies reported randomization and only 29% of published studies were blinded. Moreover, there is an absence of adequate statistical analysis for most studies and power analysis was only documented by 3% of published studies. There also appears to be significant amounts of unpublished negative or neutral data accumulated by investigators that is not reported in the literature, and this causes an overestimation of efficacy of published positive data. When data from all sources is combined, the

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net efficacy result is attenuated. It is interesting to note that there was no significant association (r^2=0.06) between the quality of science being published in journals and the impact factor of the journal, and that there was also no significant association (r^2=0.004) between the quality of science and the number of citations of a particular study article.

Based upon the findings cited above, recommendations for solid translational research, which should be duly incorporated into translational grant applications and publications reporting translational research are required. The following recommendations should ensure reproducible, valid research on an international level. As suggested by NINDS in a RIGOR report (48) coinciding with an NINDS Workshop on Improving the Quality of NINDS-Supported Preclinical and Clinical Research through Rigorous Study Design and Transparent Reporting (48), the application of fundamental principles of experimental design to preclinical research is necessary and studies should incorporate the following experimental design characteristics (Table 1):

(1) The investigator should provide sufficient **rationale for the model selection** and endpoint measurement.

(2) The studies should incorporate **justification of sample size**, including complete power analysis calculations for primary endpoints.

(3) **An adequate number of control groups** using an appropriate route of administration and timing of intervention delivery should be incorporated into the study to reflect eventual use in the patient population (i.e.: oral, intravenous, acute, chronic).

(4) The studies should be fully **randomized and blinded**.

(5) The **statistical analysis** for results interpretation should be consistent with study design. For example, if multiple groups are being compared, ANOVA with a post hoc test incorporating the Bonferonni correction may be required (Table 1).

STAIR- stroke therapy academic industry roundtable

Since 1999, translational stroke researchers have applied to some extent, a set of recommendations proposed by stroke therapy academic industry roundtable (STAIR), a collaborative effort between academics and industry [15] to develop effective stroke treatments. While STAIR suggested the possible use of rodents and primates to test treatment strategies measuring 2 outcomes, functional response and histological outcome in the acute stroke phase (1-3 days) and long-term (7-30 days), Turner et al. [16] emphasized the utility of rabbit (Oryctolagus cuniculus), a non-rodent species, to test stroke therapies because the model was used effectively for the preclinical development of tissue plasminogen activator (tPA) [16-18]. The proposal suggests that the rabbit small clot embolic stroke model be used for primary screening of therapies alone or in combination with tPA, which is a bonafide "positive control" for AIS. For additional screening, Cook and Tymianski have justified the use of nonhuman primates to effectively bridge the translational gap between animals and humans [19], but this has not been validated for any therapy.

STAIR recommends that all studies be randomized and blinded, efficacy be established in 2 or more laboratories, and efficacy should be replicated in a second species. The investigator should consider the route of administration (to administer intravenous or not) and also apply the therapy within a clinically useful therapeutic window. Subsequent STAIR recommendations (2004-2011), focused on developing neuroprotective therapies, expanding treatment options, utilizing combination therapies and designing clinical trials [20-23]. In the 2009 STAIR report [22], recommendations related to the conduct of good science or good laboratory practice were made and included eliminating randomization and assessment bias, defining inclusion and exclusion criteria for all studies, conducting full power analysis and sample size calculations and also disclosing potential conflicts of interest (Table 1).

Since translational research is an evolving science in itself, and there are still no FDA-approved neuroprotection or neurorecovery- or neurorestorative-based treatments for stroke, the exact formula for success is an unknown quantity. There have been STAIR recommendations to address co-morbidities that are recognized in AIS patients, and the need for inclusion of those co-morbidities in preclinical investigations. The STAIR committee suggested that "after initial evaluations in young, healthy male animals, further studies should be performed in females, aged animals, and animals with co-morbid conditions such as hypertension, diabetes, and hypercholesterolemia". Since the recommendations are population based, and are centered around the idea that studies in animal models with co-morbidities would better reproduce the "pathophysiological" state of patients presenting with strokes, there are quite valid, but this will require the use of an extensive number of animals that cannot easily be supported by current funding mechanisms.

Based upon the NINDS rt-PA and ECASSIII trials, the stroke patient population included in the trials were a mixed gender aged population, had a history of hypertension or diabetes, which may have been controlled by one or more prescription drug or other pharmaceutical. The majority of AIS patients are also not anti-hypertensive agent naive [24,25], and may also receive anticoagulants, statins or other treatments [24]. These points are critical to the development of a translational research program, when an investigator must utilize the "correct" animal model for drug development. There is important information available showing that the small population of diabetic patients enrolled in the NINDS rt-PA trial [26] were refractory to tPA. It is difficult to effectively treat diabetic stroke patients [27-30], since the population has been shown to be independently associated with poor neurological outcome and higher mortality in the absence of thrombolytic treatment [28-30], and diabetic patients treated with

1) **Experimental design:**
• Rationale for the selected models and endpoints
• Adequacy of the controls
• Route & timing of intervention including delivery method and dosing
• Justification of sample size, including power calculation
• Statistical methods used in analysis and interpretation of results
2) **Minimizing bias**:
• Methods of blinding (allocation concealment and blinded assessment of outcome)
• Strategies for randomization and/or stratification
3) **Results**:
• Reporting of data from attrition or exclusion, negative, neutral and positive
• Independent validation/replication, if funding is available
• Validation/replication in a second species, if funding is available
• Dose-response and therapeutic window analysis
4) **Interpretation of results**:
• Alternative interpretations of the experimental data
• Discussion of effect size in relation to potential clinical impact
• Potential conflicts of interest

Table 1: Study Design Recommendations.

tPA [26], have significantly reduced odds for favorable outcome at 3 months [17].

Considering the extensive population information discussed above, the stroke research community will need to address animal models and determine which animal model (s) best reproduce the target population. Will using a standard "drug" naive hypertensive rodent be sufficient to predict drug efficacy in a heterogeneous population of stroke patients? Should translational studies attempt to treat the diabetic population presenting with a stroke, or should "proof of concept" efficacy first be obtained for the larger mixed gender aged stroke population? clinical study in diabetics for post drug. There is no clear answer other than translational studies should incorporate young and aged mixed gender species for preliminary therapy investigation studies. Similar animal model questions will have to be addressed by the community of researchers investigating other neurodegenerative diseases.

STEPS- stem cell therapies as an emerging paradigm in stroke

The STEPS committee somewhat parallels the STAIR committee and has recommended a restorative therapy development strategy [31,32] quite similar to STAIR. Because STEPS is focused on the use of a cell-based therapy to restore function, there are only minor "technical" aspects of the STEPS recommendations that are different from STAIR recommendations. For example, STEPS also recommends testing the test therapy in multiple animal strains (species), the need to replicate studies in a second species, the investigator should take into consideration therapeutic window of the therapy and dose-response, if any. Since the target population is stroke, and the idea behind using a cell-based therapy is restoration of function, STEPS recommends measuring functional outcome at a minimum of 1 month post treatment, since the recovery response may be slow. The follow-up STEPS report [32] suggested that efficacy results should be reproduced in multiple laboratories and in at least 2 different species (Table 1). Similar to previous recommendations made above, the therapy should be studied in animal models with co-morbidities (hypertensive, diabetic) and in both ischemic and hemorrhagic stroke models. All study data (positive, neutral and negative) should be reported in publications.

Summary and Conclusions

Since there are many similarities between the recommendations of STAIR, STEPS and RIGOR, the following section will attempt to present a set of consistent guidelines or recommendations using good laboratory practices. As discussed, there are a few critical practices that should eventually be incorporated into all scientific studies to reflect study group blinding, study group randomization, and complete power analysis and statistical analysis (Table 1). It is recommended that these criteria should be incorporated into translational grant applications and manuscripts submitted to the Journal of Neurology and Neurophysiology (Table 2). A conflict of interest statement is required for all investigators on the study, and this should include funding sources for the study (government, private, and industry), collaborations with industry, membership on scientific or clinical advisory boards, and financial interest in the industry broadly related to current work.

Guideline Criteria	Yes	No
Randomized		
Blinded		
Power Analysis		
Statistical Analysis		
Justification of Model		
All data are being reported		
Conflict of Interest Statement		

Table 2: Author RIGOR Criteria Adherence.

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Conflict of Interest

There are no conflicts of interest to disclose. PAL is Editor-in-Chief of JNN and a Chartered Member of National Institute of Neurological Disorders and Stroke Study Section NSD-A.

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