Optimization of the decision-making process for the selection of therapeutics to undergo clinical testing for spinal cord injury in the North American Clinical Trials Network

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The North American Clinical Trials Network (NACTN) includes 9 clinical centers funded by the US Department of Defense and the Christopher Reeve Paralysis Foundation. Its purpose is to accelerate clinical testing of promising therapeutics in spinal cord injury (SCI) through the development of a robust interactive infrastructure. This structure includes key committees that serve to provide longitudinal guidance to the Network. These committees include the Executive, Data Management, and Neurological Outcome Assessments Committees, and the Therapeutic Selection Committee (TSC), which is the subject of this manuscript. The NACTN brings unique elements to the SCI field. The Network’s stability is not restricted to a single clinical trial. Network members have diverse expertise and include experts in clinical care, clinical trial design and methodology, pharmacology, preclinical and clinical research, and advanced rehabilitation techniques. Frequent systematic communication is assigned a high value, as is democratic process, fairness and efficiency of decision making, and resource allocation. This article focuses on how decision making occurs within the TSC to rank alternative therapeutics according to 2 main variables: quality of the preclinical data set, and fit with the Network’s aims and capabilities. This selection process is important because if the Network’s resources are committed to a therapeutic, alternatives cannot be pursued. A proposed methodology includes a multicriteria decision analysis that uses a Multi-Attribute Global Inference of Quality matrix to quantify the process. To rank therapeutics, the TSC uses a series of consensus steps designed to reduce individual and group bias and limit subjectivity. Given the difficulties encountered by industry in completing clinical trials in SCI, stable collaborative not-for-profit consortia, such as the NACTN, may be essential to clinical progress in SCI. The evolution of the NACTN also offers substantial opportunity to refine decision making and group dynamics. Making the best possible decisions concerning therapeutics selection for trial testing is a cornerstone of the Network’s function.

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KEY WORDS • spinal cord injury • clinical trial • therapeutics • North American Clinical Trials Network • decision making • consensus

THE NACTN is a unique collaborative entity that is not tied to a business strategy or a particular investigator’s research program. This uniqueness of the NACTN has created an unusual opportunity for impartiality in decision making. The first Phase I neuroprotection trial within the Network completed clinical enrollment in June of 2011 using the off-patent drug riluzole (Sanofi-Aventis). The Network plans to increase the capacity to conduct trials and requires that its resources are optimally used. The prioritization of potential therapeutic candidates for NACTN testing is the task of the TSC. The subject of this article is how the TSC function is structured to optimize its efficacy and impartiality. In addition, we propose a methodology to make evaluation and selection of therapeutics more rational, quantitative, and less biased.

The mission statement of NACTN is “to carry out clinical trials of the comparative effectiveness of new therapies for SCI using an established consortium of neurosurgery departments at university-affiliated civilian medical center hospitals and military hospitals with medical, nursing and rehabilitation personnel who are

Abbreviations used in this paper: NACTN = North American Clinical Trials Network; SCI = spinal cord injury; TSC = Therapeutic Selection Committee.
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skilled in the evaluation and management of SCI.” Goals of NACTN relevant to the TSC are to “develop a mechanism to solicit and rigorously assess potential therapies and prioritize interventions to be tested” and “test promising therapies for SCI in rigorous clinical trials that are designed to ensure interpretable, meaningful data and safety for the patients undergoing treatment.”

North American Clinical Trials Network standing committees are formed by the Executive Committee to address long-term issues critical to the goals and objectives of NACTN by developing policies and procedures to meet established goals, which are presented to the site principal investigators for approval. The committee chair is responsible for ensuring an organized agenda and that succinct minutes are recorded for every meeting. All documents (including agendas and minutes) are uploaded to the NACTN file transfer protocol site.

Purpose of the NACTN

The mandate of the NACTN TSC is to establish a Treatment Strategy Selection Committee to solicit and/or otherwise identify potential new SCI therapeutics, review the animal preclinical and available clinical data, and formulate a recommendation to the Executive Committee as to whether NACTN should consider testing a particular intervention in a clinical trial.

Membership of the TSC

The committee will be comprised of a minimum of 2 site principal investigators with particular knowledge of translational research and clinical trials in SCI. Additionally, the committee would invite basic scientists to participate ad hoc, depending on the therapies under consideration.

Goals of the TSC

The goals of the TSC are: 1) establish a mechanism by which to identify and evaluate potential therapies for NACTN to test in clinical trials, including from within the NACTN, but also from academia and the pharmaceutical and biologics industry; and 2) use non-NACTN expertise by reaching out to appropriately qualified investigators in basic and translational science to provide input regarding prospective therapeutics.

Structure and Processes of the TSC

Evolutionary Process

The main purpose of the TSC is to carefully evaluate, discuss, and rank potential therapeutics and to make recommendations to the executive committee regarding the best options for NACTN to pursue. The primary steps of the TSC internal process are: 1) assemble and tabulate evaluation criteria; 2) assemble and tabulate therapeutics according to classes; 3) prioritize the therapeutics by classes and within classes; 4) seek additional input as needed; 5) refine the prioritization; and 6) make recommendations to the executive committee (Fig. 1).

Sources of Information. The primary information sources for the TSC are peer-reviewed publications within the scientific literature. In addition to this source, presentations at conferences are also considered. If appropriate, other communications and data may be discussed as arises when the NACTN is contacted by representatives of academia or industry who are proponents of specific therapeutics. There is also the collective experience of the group, members of which have been involved with SCI trials over several decades, and their ongoing connections to many facets of neurotrauma therapeutics.

Committee Structure. Currently the TSC is comprised of 8 persons from 7 separate institutions. There are 6 neurosurgeons, 3 of whom have extensive experience in preclinical SCI models and therapeutics testing. Additionally, there is a senior expert neuroscientist and an expert advisor from the NIH. The committee includes members with an understanding of SCI at an expert level that spans mechanistic biology to clinical trials and their analysis.

Decision-Making Process

Committee Meetings. The majority of meetings are held by conference call and follow an agenda that is circulated by the Chairperson or designate. Calls have an allotted time period, typically 50–80 minutes. Notes are taken manually by the chairperson, who creates minutes that are subsequently circulated to the committee members in a timely manner. An agenda is prepared by the committee chairman in consultation with committee members to address new business and to follow through on unresolved issues recorded in prior minutes. As new therapies arise they are thoroughly reviewed, and if found to be favorable, incorporated into the existing therapeutics ranking.

Conference Call Process. All persons on the call are identified during a role call by the chairperson and introductions, if appropriate, are made. The minutes of the prior session are discussed with request for correction of errors, oversights, or omissions. Then the minutes are accepted by nomination and seconding. The first agenda item is introduced and input is invited. An effort is made to obtain input from all members, and interruptions are avoided unless the discussion goes off topic or is excessive in the view of the chair, who then interjects. At the close of discussion of the topic, 1 member provides a summary, and an action item is proposed. At this point, a consensus is sought and any significant objection results in additional discussion or re-tabling of the issue. Two committee members may be assigned to gather further data, or communicate with academic or industry sources, and report back to the committee. During the committee meeting, other parties may present information to the committee by joining the conference call at a scheduled time. These discussions are confidential.

Identification of Therapeutics. The first step in the evaluative process was to make distinctions between classes of therapeutics including drugs, cells, engineered biologics, and physical methods such as neural stimulation, hypo-
thermia, and CSF drainage. Combination therapies, such as combinations of different classes of therapeutics and advanced rehabilitation strategies, are considered in discussion with colleagues from the Neurorecovery Network. The Neurorecovery Network works closely with NACTN.

**Evaluation of the Strengths and Weaknesses of the Case for Translation of a Therapeutic Within NACTN**

The strengths and weaknesses of the assembled preclinical information for each therapeutic is discussed with reference to published guidelines that recommend criteria as detailed in Criteria Set 1 below. After criteria are selected they can be later ranked and weighted. Criteria Set 1, for preclinical data, is as follows: 1) relevant animal SCI model(s); 2) relevant timing of intervention; 3) clinically feasible delivery method; 4) optimization of dose, duration of therapy, and therapeutic window; 5) relevant outcome assessments that provide persuasive evidence of safety and efficacy; 6) independent replication; and 7) readiness for clinical translation. It is important to note that the evaluation of the extent to which a therapeutic’s data set satisfies these criteria has both quantitative and qualitative components.

For therapeutics that have undergone prior clinical testing, the following additional criteria (Criteria Set 2, clinical data) are considered: 1) quality of the research design, such as randomization, controls, blindedness, study power, and outcome procedures employed; 2) relevance to SCI; 3) regulatory status; 4) degree of invasiveness and risk; 5) extent and quality of follow-up data, especially safety data; and 6) standardization of therapeutic and procedures.

The fit with NACTN resources involves assessing the following criteria (Criteria Set 3, NACTN variables): 1) fit with NACTN priorities and principles; 2) timing of availability for clinical testing; 3) cost and possible funding for clinical testing; 4) proposed duration of the study; 5) suitability for multicenter study at NACTN centers; and 6) requirement for specialized rehabilitation.

Two variables predominantly influence the ranking process. The overall quality of the case for translation of the therapeutic is based on the extent to which the criteria in Sets 1–2 are satisfied and the potential fit with NACTN resources (Criteria Set 3). For example, the NACTN does not have the resources to develop new therapeutics, fund preclinical research, pay consultants, and conduct device development, nor are these aims of the NACTN. Thus, these issues need to have been settled prior to consideration for testing in the NACTN. A therapeutic may have very impressive scientific merits, such as those for chondroitinases, but not be suitable for testing in the Network until the pragmatic issues of developing a refined clinical product and regulatory status are resolved. It is understood that the highest ranked therapeutics are those that will be recommended for translation within NACTN. Thus, it is not the intent of the ranking process to select those options that are theoretically optimal, but those that are pragmatic, feasible, and likely to be safe.

The problem that the committee has to solve is how to evaluate therapeutics across multiple discrete variables and individual opinions. The ranking and evaluation process that the committee is working toward is a form of multiattribute decision making, in which multiple criteria are selected, then ranked, and then assigned a weight to allow creation of actual scores. The 3 dimensions of the criteria—preclinical, clinical, and NACTN-focused—can be integrated into a table/matrix, and the next step in the proposed process is the assignment of a percentile score that indicates the extent to which the committee believes that a therapeutic satisfies the criteria. It is understood that no therapeutic alternative will fully satisfy all criteria. The goal is to reach an optimal decision based on available information and the committee members’ individual and collective competence. It is further recognized that the facts on which translation is predicated are imperfect. Thus, a degree of judgment must be exercised.

**Current Feasible Therapeutics**

Currently feasible therapeutics for neurosurgical clinical trials can be classified into 6 lists (classes): 1) drugs, such as riluzole; 2) engineered biological molecules, such as BA-210 (Cethrin; Alseres Pharmaceuticals, Inc.); 3) cells, such as Schwann cells; 4) biopolymer scaffolds, such as polyglycolic acid; 5) physiological methods, such as hypothermia and CSF drainage; and 6) neural...
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stimulation and recording, such as epidural stimulation. Combination therapies, such as combinations of different classes of therapeutics and advanced rehabilitation strategies, are considered in discussion with colleagues from the Neurecovery Network, which works closely with the NACTN.

In the proposed decision strategy, the 3 sets of criteria are ranked/prioritized based on both the evident scientific strength, and pragmatic fit with the Network’s capabilities and needs, using repeated pairwise comparisons. The prioritization method will consist of ranking the parameters from most important to least important, using the value criterion that the most important variables were those that if not satisfied, would be negative for further consideration of the therapeutic, such as lack of persuasive evidence of safety and efficacy. Thus, the lowest ranked criteria are those that could be absent but not exclude the therapeutic from further consideration, such as lack of independent replication. The ranked preclinical criteria for the TSC internal process are as follows; 1) relevant outcome assessments that provide persuasive evidence of safety and efficacy; 2) relevant animal SCI model(s); 3) clinically feasible delivery method; 4) “readiness” for clinical translation; 5) optimization of dose, duration, or therapy, and therapeutic window; 6) relevant timing of intervention; and 7) independent replication.

In a similar manner, the clinical criteria are also ranked in order of importance to a potential trial within NACTN. The ranked clinical criteria for the TSC internal process are: 1) relevance to SCI; 2) quality of the prior research design, such as randomization, controls, blinding, study power, and outcome measures employed; 3) degree of invasiveness and risk; 4) extent and quality of follow-up data, especially safety data; 5) standardization of therapeutic and procedures; and 6) regulatory status.

The NACTN-focused criteria are also ranked in order of importance: 1) fit with NACTN priorities and principles; 2) suitability for multicenter study at NACTN centers; 3) cost and possible funding sources or industry sponsorship; 4) timing of availability for clinical testing; 5) proposed duration of the study; and 6) requirement for specialized rehabilitation.

After the ranking was performed by pairwise comparison, it was decided to assign the attribute a relative weight to generate rank-order centroids consistent with the Multi-Attribute Global Inference of Quality technique as described by McCaffery and Koski.11 Finally, the decision matrix (Table 1) is constructed by assigning a percentage score from 1 to 100, based on the extent to which the therapeutics data set fulfilled each weighted criteria (fulfillment range). The weighted criteria are then multiplied by the percentage to generate a number that is useful for relative comparison between candidate therapeutics. When summated, these numbers provide an estimate of the relative strength of one candidate therapeutic as opposed to another.

Some of the criteria, such as requirement for specialized rehabilitation, (long) duration of study, and degree of invasiveness and risk, are assigned a high percentage if they are less burdensome; that is, sophisticated rehabilitation, multiyear studies, and highly invasive therapies put more strain on Network resources and require very careful consideration before committing to them.

This decision matrix was tested for 2 representative proposed therapeutics: Schwann cells (Table 2) and minocycline (Table 3). These proposed therapeutics were selected because there is extensive preclinical data for both, as well as some clinical data.

**Initial Summary of the Test Review of Schwann Cells**

Schwann cells have been extensively studied for transplantation in SCI at acute2,6,12,13,19 and chronic stages. A clinical trial of Schwann cells for SCI has been published that was completed in Iran.17,18,22 As an autologous cell therapy, immune suppression may not be required (reducing risk), but each preparation represents an independent workload that must be uniquely characterized, in contrast to the use of allografted cell lines that may be derived from a cell bank.

The evaluation of Schwann cells according to our criteria was as follows: 1) relevant outcome assessments that provide persuasive evidence of safety and efficacy: yes. Schwann cells have been studied in contusion models of SCI, and a limited number of preclinical studies have assessed safety; 2) relevant animal SCI model(s): yes, cervical and thoracic models of spinal cord contusion, in several species; 3) clinically feasible delivery method: yes, direct spinal cord injection is feasible; 4) “readiness” for clinical translation: yes, autologous Schwann cell preparations could be transplanted into patients; 5) optimization of dose, duration, or therapy, and therapeutic window: no, these issues have been incompletely resolved; 6) relevant timing of intervention: yes, several times points have been tested; 7) independent replication: yes, a preclinical study replicated a finding of efficacy after SC transplantation; 8) relevance to SCI: yes; 9) quality of the prior (clinical) research design, such as randomization, controls, blinding, study power, and outcome measures employed: moderate; 10) degree of invasiveness and risk: high, because Schwann cell transplantation requires a repeat surgery and direct injection into the spinal cord, and potential risks are considerable; 11) extent and quality of follow-up data, especially safety data: moderate; 12) standardization of therapeutic and procedures: yes; 13) regulatory status: pending; 14) fit with NACTN priorities and principles: yes; 15) suitability for multicenter study at NACTN centers: complex; 16) cost and possible funding sources or industry sponsorship: there is currently no industry source to fund such a trial; 17) timing of availability for clinical testing: Schwann cells could be tested now; 18) proposed duration of the study: at least 1 year follow-up, and longer imaging follow-up; and 19) requirement for specialized rehabilitation: not required but likely to be contributory.

**Minocycline: Initial Summary of the Review**

A tetracycline antibiotic that was discovered to have potent antiinflammatory activity, minocycline has been studied in several human CNS diseases including stroke, multiple sclerosis,25 AIDS dementia,2 and Parkinson disease.15,16 Minocycline was studied in an early phase clinical trial in Canada subsequent to reports of benefit
in animal SCI studies. Clinical results from the SCI trial have been presented at conferences but are not yet published. Neither the preclinical or clinical data show unequivocal benefit.

The evaluation of minocycline according to our criteria was as follows: 1) relevant outcome assessments that provide persuasive evidence of safety and efficacy; yes; 2) relevant animal SCI model(s); yes; 3) clinically feasible delivery method; yes; 4) “readiness” for clinical translation; yes; 5) optimization of dose, duration, or therapy,

### TABLE 1: Decision matrix*

<table>
<thead>
<tr>
<th>Preclinical Variable</th>
<th>Wt</th>
<th>%</th>
<th>Clinical Variable</th>
<th>Wt</th>
<th>%</th>
<th>NACTN Variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>relevant outcome assessments that provide persuasive evidence of safety &amp; efficacy</td>
<td>0.21</td>
<td>80</td>
<td>relevance to SCI</td>
<td>0.26</td>
<td>80</td>
<td>fit with NACTN priorities &amp; principles</td>
</tr>
<tr>
<td>relevant animal SCI model(s)</td>
<td>0.18</td>
<td>90</td>
<td>quality of the research design, such as randomization, controls, blinding, study power, &amp; outcome measures employed</td>
<td>0.23</td>
<td>40</td>
<td>suitability for multicenter study at NACTN centers</td>
</tr>
<tr>
<td>clinically feasible delivery method</td>
<td>0.16</td>
<td>90</td>
<td>degree of invasiveness &amp; risk</td>
<td>0.18</td>
<td>10</td>
<td>cost &amp; possible funding for clinical testing</td>
</tr>
<tr>
<td>readiness for clinical translation</td>
<td>0.14</td>
<td>90</td>
<td>extent &amp; quality of follow-up data, especially safety data</td>
<td>0.16</td>
<td>50</td>
<td>timing of availability for clinical testing</td>
</tr>
<tr>
<td>optimization of dose, duration of therapy, &amp; therapeutic window</td>
<td>0.12</td>
<td>50</td>
<td>standardization of therapeutic &amp; procedures</td>
<td>0.10</td>
<td>50</td>
<td>proposed duration of the study</td>
</tr>
<tr>
<td>relevant timing of intervention</td>
<td>0.10</td>
<td>70</td>
<td>regulatory status</td>
<td>0.07</td>
<td>70</td>
<td>requirement for specialized rehabilitation</td>
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<tr>
<td>independent replication</td>
<td>0.09</td>
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<tr>
<td>sum of scores</td>
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<td>100</td>
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<td>1.0</td>
<td>100</td>
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</tr>
</tbody>
</table>

* Total score.

### TABLE 2: Decision matrix for Schwann cells*

<table>
<thead>
<tr>
<th>Preclinical Variable</th>
<th>Wt</th>
<th>%</th>
<th>Clinical Variable</th>
<th>Wt</th>
<th>%</th>
<th>NACTN Variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>relevant outcome assessments that provide persuasive evidence of safety &amp; efficacy</td>
<td>0.21</td>
<td>80</td>
<td>relevance to SCI</td>
<td>0.26</td>
<td>80</td>
<td>fit with NACTN priorities &amp; principles</td>
</tr>
<tr>
<td>relevant animal SCI model(s)</td>
<td>0.18</td>
<td>90</td>
<td>quality of the research design, such as randomization, controls, blinding, study power, &amp; outcome measures employed</td>
<td>0.23</td>
<td>40</td>
<td>suitability for multicenter study at NACTN centers</td>
</tr>
<tr>
<td>clinically feasible delivery method</td>
<td>0.16</td>
<td>90</td>
<td>degree of invasiveness &amp; risk</td>
<td>0.18</td>
<td>10</td>
<td>cost &amp; possible funding for clinical testing</td>
</tr>
<tr>
<td>readiness for clinical translation</td>
<td>0.14</td>
<td>90</td>
<td>extent &amp; quality of follow-up data, especially safety data</td>
<td>0.16</td>
<td>50</td>
<td>timing of availability for clinical testing</td>
</tr>
<tr>
<td>optimization of dose, duration of therapy, &amp; therapeutic window</td>
<td>0.12</td>
<td>50</td>
<td>standardization of therapeutic &amp; procedures</td>
<td>0.10</td>
<td>50</td>
<td>proposed duration of the study</td>
</tr>
<tr>
<td>relevant timing of intervention</td>
<td>0.10</td>
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<td>regulatory status</td>
<td>0.07</td>
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<td>requirement for specialized rehabilitation</td>
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<td>independent replication</td>
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<td>1.0</td>
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<tr>
<td>sum of scores</td>
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<td>100</td>
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<td>1.0</td>
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</table>

* Total score: 179.2.
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TABLE 3: Decision matrix for minocycline*

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<tr>
<th>Preclinical Variable</th>
<th>Wt %</th>
<th>Wt × %</th>
<th>Clinical Variable</th>
<th>Wt %</th>
<th>Wt × %</th>
<th>NACTN Variable</th>
<th>Wt %</th>
<th>Wt × %</th>
</tr>
</thead>
<tbody>
<tr>
<td>relevant outcome assessments that provide persuasive evidence of safety &amp; efficacy</td>
<td>0.21</td>
<td>80</td>
<td>relevance to SCI</td>
<td>0.26</td>
<td>90</td>
<td>fit w/ NACTN priorities &amp; principles</td>
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<td>90</td>
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<tr>
<td>relevant animal SCI model(s)</td>
<td>0.18</td>
<td>90</td>
<td>quality of the research design, such as randomization, controls, blinding, study power, &amp; outcome measures employed</td>
<td>0.23</td>
<td>70</td>
<td>suitability for multicenter study at NACTN centers</td>
<td>0.21</td>
<td>90</td>
</tr>
<tr>
<td>clinically feasible delivery method</td>
<td>0.16</td>
<td>100</td>
<td>degree of invasiveness &amp; risk</td>
<td>0.18</td>
<td>80</td>
<td>cost &amp; possible funding for clinical testing</td>
<td>0.19</td>
<td>70</td>
</tr>
<tr>
<td>readiness for clinical translation</td>
<td>0.14</td>
<td>100</td>
<td>extent &amp; quality of follow-up data, especially safety data</td>
<td>0.16</td>
<td>50</td>
<td>timing of availability for clinical testing</td>
<td>0.11</td>
<td>100</td>
</tr>
<tr>
<td>optimization of dose, duration of therapy, &amp; therapeutic window</td>
<td>0.12</td>
<td>60</td>
<td>standardization of therapeu tic &amp; procedures</td>
<td>0.10</td>
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<td>proposed duration of the study</td>
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</tr>
<tr>
<td>relevant timing of intervention</td>
<td>0.10</td>
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<td>regulatory status</td>
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<td>requirement for specialized rehabilitation</td>
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<td>independent replication</td>
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* Total score: 231.4.

and therapeutic window: moderate; 6) relevant timing of intervention: yes; 7) independent replication: yes; 8) relevance to SCI: yes; 9) quality of the prior research design, such as randomization, controls, blinding, study power, and outcome measures employed: good; 10) degree of invasiveness and risk: low; 11) extent and quality of follow-up data, especially safety data: good from cumulative studies in several proposed indications; 12) standardization of therapeutic and procedures: yes; 13) regulatory status: approved for use in infectious diseases; 14) fit with NACTN priorities and principles: yes; 15) suitability for multicenter study at NACTN centers: yes; 16) cost and possible funding sources or industry sponsorship: inexpensive drug, no industry funding source; 17) timing of availability for clinical testing: now; 18) proposed duration of the study: 6 months to 1 year; and 19) requirement for specialized rehabilitation: no.

In these 2 examples, low cost of the treatment, low invasiveness, shorter study duration, and lack of requirement for specialized rehabilitation were perceived as factors of benefit for a study within the network. These issues favored a simpler neuroprotective drug therapy over a more complex autologous cell therapy.

Discussion

Value of Constraining the Decision-Making Process to Specific Criteria

Although in an expert discussion the group may develop a sense of the relative strengths of candidate therapeutics, there are a number of reasons to provide a formal basis for the decision process. The first reason is to reduce arbitrariness, the second is to constrain subjectivity, and the third is to create a record of how an evaluation decision was made. Further, as new information regarding a therapeutic is acquired, it would be a more rational way to amend the evaluation matrix.

Subjective Aspects of Decision Making

It is difficult to remove subjectivity from this process. In science, subjectivity is regarded as undesirable, but in decision making among experts, there are numerous intangible aspects of the experts’ background knowledge and experience that serve to create their expertise. After all, if a fully objective process were available there would be little need for opinion, other than an opinion of the value of the decision process algorithm. One important factor in evaluating the case for a therapeutic is the degree to which an expert is truly convinced, which involves evaluating the difference between claims and evidence.

Strengths and Weaknesses of Consensus-Based Decision Making

The TSC arrives at a ranking of available therapeutics through consensus; that is, through discussion and debate in a noncoercive cooperative manner to achieve decisions that best satisfy the committee member’s opinions. Consensus decision making has a long history and has been extensively researched in the psychological and management fields. There are known strengths and weaknesses as listed in Table 4. Alternative methods to arrive at a decision are compromise, majority vote, decision by the group leader, and arbitration. However, these are not optimal in the context of expert discussion. Consensus re-
Groupthink occurs when the desire for harmony overrides a critical examination of alternatives that may involve some level of discord. Maintenance of ability to dissent or disagree is pivotal to the utility of consensus decision making. The committee attempts to recognize sources of potential bias that might preclude optimal evaluation and decision making (Table 5). Because TSC members are quite homogenous in background and experience, there is a risk of a form of rationalized conformity, known as "groupthink." "Groupthink occurs when the desire for harmony overrides a critical examination of alternatives that may involve some level of discord. Maintenance of ability to dissent or disagree is pivotal to the utility of evaluative committees when backgrounds are homogenous. The Abilene paradox occurs when the selected alternative is not the preference of any group member, but due to a sense of consensus pressure, group members avoid raising their viewpoint, resulting in a selection of a suboptimal alternative.

Conclusions

The NACTN provides a framework in which consensus decision making is highly valued. The ability to evaluate a potential treatment systematically across many variables enhances the function of the TSC. The proposed methodology will be tested in future committee evaluations.

Disclosure

Dr. Fawcett serves as a consultant to Acorda Therapeutics and Covidien. This study was supported by the Telemedicine and Advanced Technology Research Center (TATRC), United States Army Medical Research and Materiel Command (USAMRMC), and awards W81XWH-07-1-0361 and W81XWH-10-2-0042. Dr. Guest is co-principal investigator on an Investigational New Drug application for Schwann cell transplantation that has been submitted to the US FDA. Author contributions to the study and manuscript preparation include the following. Conception and design: Guest, Tator. Analysis and interpretation of data: Guest, Tator. Drafting the article: Guest, Aarabi. Critically revising the article: Guest, Harrop, Grossman, Fehlings, Tator, Fawcett. Reviewed submitted version of manuscript: Fawcett.

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TABLE 4: Strengths and weaknesses of consensus-based decision making

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>democratic</td>
<td>may be tedious</td>
</tr>
<tr>
<td>inclusive</td>
<td>may overvalue less informed point of view</td>
</tr>
<tr>
<td>uses full available expertise &amp; opinion resources</td>
<td>subject to known serious biases such as groupthink &amp; the Abilene paradox</td>
</tr>
<tr>
<td>may result in decisions w/ broad support</td>
<td></td>
</tr>
</tbody>
</table>

Table 5: Methods to reduce bias in TSC process

| balanced membership | declaration of all potential conflicts of interest |
| framing the discussion according to published standards & recommendations | avoidance of secrecy & offline conversations |
| detailed minutes | monthly reporting to NACTN membership during monthly conference calls |

TABLE 5: Methods to reduce bias in TSC process

Discloses potential conflicts of interest.
Selecting therapeutics for clinical testing in SCI


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