

Studying the Liberation Procedure for Multiple Sclerosis (MS) CALL FOR PROPOSALS - December 17, 2010

1. Background and Purpose of the Call

Decreased blood flow caused by blockage of veins is thought to lead to iron accumulation in the brain, which may trigger an inflammatory response leading to MS. This is still a theory. The “liberation” procedure uses angioplasty to open veins in the neck and chest and is intended to increase blood flow from the brain and spinal cord. Throughout Canada and in Saskatchewan, there is strong pressure from patients and their families to have access to the “liberation” procedure – it is inspiring hope because of reports of MS patients experiencing relief from their symptoms after the procedure. However, there is controversy about this new procedure, leading experts to be cautious about proceeding.

There are many unknowns about the liberation procedure and the condition it is designed to treat, known as chronic cerebrospinal venous insufficiency (CCSVI). For example, how many MS patients have this condition? What role does CCSVI play in MS? Does the liberation procedure work, and, if so, for how long? What are its risks and costs versus benefits? Are the techniques used in angioplasty of veins appropriate and effective? Is there a particular subtype of MS or stage of MS disease progression that responds to the liberation treatment while other forms or stages of MS are non-responsive? Is CCSVI found in other diseases and syndromes of the brain?

Undertaking research that can provide answers to some of the many questions about the “liberation” procedure would be a great service to MS sufferers and their health-care providers. If the procedure proves to be safe, effective and feasible, it could be offered to patients sooner, improving their quality of life and possibly reducing the need for other health services.

In late July 2010, the Premier of Saskatchewan announced that the Province was willing to fund clinical trials of the new Zamboni “liberation” procedure for people with MS, and would be looking to the research community for proposals to answer this research question: Is the “liberation” procedure a safe and effective treatment for MS patients to provide relief of symptoms and improve quality of life?

Clinical trials are an important type of research needed to answer this question. A well designed clinical trial will take into account findings from ongoing research, will address safety and ethical issues, and may involve a phased approach, if appropriate.

2. Funding Envelope

SHRF will provide up to five million dollars for up to five years. It is expected that only one research proposal will be funded.

The successful proposal will focus on Saskatchewan patients; however, research teams submitting proposals are welcome to include partners with funding from other jurisdictions to expand the study to include patients from those jurisdictions.

3. Important Dates

Letters of Intent (LOI) are due to SHRF by 4:30 p.m. Central Standard Time, January 31, 2011.

Full proposals are due to SHRF by 4:30 p.m. Central Standard Time, March 28, 2011.

Scientific peer review will be completed in mid-April, 2011.

Funding decisions will be announced in late-April, 2011. The successful research team will begin its study as soon as all ethical and operational approvals are in place - ideally late-spring, 2011.

4. Eligibility Requirements

The following requirements must be met by all applicants to be eligible for funding. Eligibility must be demonstrated at the LOI stage.

- The research team will include clinicians and scientists comprising expertise in designing and managing effective and appropriate clinical trials, providing medical care for patients with MS, and leading a multi-disciplinary, multi-site research team.
- Team members will have a demonstrated record of excellence in their fields.
- The call for proposals is open to researchers from across Canada; a portion of the research team will be from Saskatchewan, including someone with a faculty appointment at one of Saskatchewan's universities who is eligible to hold research grants at that institution.
- The research design will be sufficiently powered to evaluate the safety, efficacy and feasibility of the MS "liberation" treatment using sound and ethical scientific processes.
- The funding provided by Saskatchewan must focus on Saskatchewan patients; a strategy to enroll Saskatchewan patients will be identified.

5. Guidelines for LOI Submission

Send (1) the original signed paper copy of the LOI, (2) six paper copies, plus (3) a copy on CD (pdf format) to:

Saskatchewan Health Research Foundation
253-111 Research Drive
Atrium Building, Innovation Place
Saskatoon, SK, S7N 3R2

Use standard letter-quality type (e.g., Times 12-point) and maintain page margins of one inch on standard 8.5 x 11 inch paper. Single-spacing may be used but at no more than 6 lines per inch. These standards are set to ensure readability for reviewers.

6. LOI Requirements

A Letter of Intent is required to notify SHRF of the intended proposal, to allow SHRF time to work with the applicant(s) to ensure eligibility requirements are met, and to provide SHRF's scientific review panel an opportunity to provide feedback to the applicant(s) before moving to a full proposal.

The LOI should be no more than 8 pages and must be signed by the principal investigator(s). The LOI should address the following items:

- Brief description of the research team, including location of members, roles and responsibilities
- List of key questions this study will address
- Brief description of approach to a clinical trial, including the intended protocol design and phases, as appropriate
- Description of controls that will be in place
- Obtaining ethical approvals
- Strategy for recruiting study subjects
- Outline of plan to access required facilities, equipment, and health care services
- Key research and/or funding partnerships or collaborations being pursued
- Identification of any potential conflicts of interest with the process or outcome of the proposed study for research team members, key partners or collaborators. If none exist, please state that.

7. Guidelines for Full Proposal Submission

7.1 Submitting the proposal

Send (1) the original signed paper copy of the proposal, (2) six paper copies (including CVs and all appended information), plus (3) a copy on CD (pdf format) to:

Saskatchewan Health Research Foundation
Atrium Building, Innovation Place
253-111 Research Drive, Saskatoon, SK, S7N 3R2

Incomplete proposals may be declared ineligible. All required documentation, including CVs and letters of support, must be attached to the application.

7.2 Presentation Requirements

Use standard letter-quality type (e.g., Times 12-point) and maintain page margins of one inch on standard 8.5 x 11 inch paper. Single-spacing may be used but at no more than 6 lines per inch. These standards are set to ensure readability for the reviewers. The principal investigator's surname is to appear in the top-right page header of every page. Page numbers are to appear in the lower-right footer as "page X of X".

8. Full Proposal Requirements

Proposals need to include a detailed research plan based on current evidence, statistical and ethical considerations, a description of the research team's expertise, a detailed budget for doing the work proposed, letters of support regarding operational needs (including health-care services and equipment needs), and plans to share research findings with the public, health care providers, and the health research community. Each requirement is listed below in detail.

8.1 Title Page

Use Appendix A - Title Page Template.

8.2 Signature Page

Use Appendix B - Signature Page Template. You may submit multiple signature pages. Original or faxed signatures will be accepted. SHRF does not accept electronic signatures. The signature page includes signatures from the Principal Investigator(s) and Co-Investigator(s), as well as the Principal Investigator's Department Head (where applicable), Dean or Director, and Research Services Office.

8.3 Research Description

Please use up to **twenty-five (25)** pages to describe your project, using the sections and topics outlined below. This page limit includes any images, figures, tables, graphs, and timelines. References and any letters of support may be appended in addition to the page limit. Please note that recruitment must focus on Saskatchewan patients, unless additional funding exists to expand recruitment to other jurisdictions.

8.3.1 Lay Summary

Using about 250 words, summarize your proposed plans in simple language that may be easily read by a general audience. Please include: overall purpose and approach, objectives for each phase, summary of key protocols, composition of the research team, and location of the research work and study subjects.

8.3.2 Research Plan

- **current state of knowledge** on CCSVI and the “liberation” treatment
- **research plan** including phases and objectives, approaches, definitions, and outcomes
- **discussion of research protocol** including but not exclusive to: inclusion/exclusion criteria, subject recruitment, beneficence and non-maleficence, risk benefit analyses, placebo control, safety, statistics, and reporting of adverse events
- plans to meet national and international **scientific standards**, including incorporating findings from ongoing studies related to CCSVI and the “liberation” treatment
- anticipated **safety and ethical issues** and plans to address them, ensuring that local and national ethical standards are met
- **anticipated challenges** (e.g., subject recruitment and retention, system capacity) and plans to overcome them
- plan and justification for placebo subjects to **cross over** to treatment group should treatment prove to be beneficial

8.3.3 Infrastructure

- **institutional support** (financial and other commitments) from research and health care institutions, noting what is available to the team and what will be developed or acquired; and
- **research environment** (space, equipment, and other support necessary to do the research), noting what is available to the group and what will be developed or acquired
- **access to patient populations for enrolling subjects**

8.3.4 Research Team and Partnerships

- **roles and responsibilities** of research team members in relation to the research plan
- **roles and contributions** of collaborators (letters of support must be included with the application)

- how the team will develop both **synergy and integration** to establish itself as a cohesive research team
- **strategic partnerships** with organizations, major stakeholders, and/or funding partners (letters of support must be included with the proposal)

8.3.5 Deliverables and Milestones

Clearly outline milestones and deliverables for each phase of the grant using the Gantt chart template provided (Appendix C). Annual reporting will include progress reports in reference to specified milestones and deliverables.

8.3.6 Knowledge Translation and Exchange Activities

Outline how you will share your results widely to ensure findings are made available to influence the care and treatment of MS patients. Target audiences to keep in mind when developing your plans should include the scientific community, care providers, patients and families, MS societies (provincial and national), government, and the public.

8.4 Budget and Expenditures Justification

Use Appendix D – Budget and Justification Template. Eligible expenses are:

- salaries for project co-ordinator/manager (recommended)
- research staff, including technicians, clinical staff, and assistants
- limited release-time for team members to increase their research focus, if necessary
- materials and supplies
- required services and technical contracts
- reimbursement of clinical care costs
- essential major equipment (including operating and maintenance)
- travel to support the research, including patient participation
- team meetings and communication
- costs of linkage and outreach to disseminate research findings, particularly with individuals and organizations committed to applying research for the improvement of health and health care

8.5 Letters of Support

Provide letters from collaborators and formal partners, and to indicate institutional and operational support for access to and use of facilities, personnel, equipment, and study subjects.

8.6 Canadian Common CVs

All principal investigators and co-investigators are to append CVs to the application, using the Canadian Common CV (CCV), accessible from SHRF's website. The accomplishments, roles and

responsibilities of collaborators and partners should be described in 8.4.3. Complete all of the CCV requirements as well as the SHRF-specified fields, then validate and print. You may access the CCV through SHRF's website: www.shrf.ca. Step-by-step instructions for completing and printing the SHRF Canadian Common CV are below.

Steps for completing and submitting the SHRF CCV:

- Access the Canadian Common CV at www.shrf.ca
- Ensure your pop-up blocker is disabled.
- Complete all sections in the CCV (e.g., identification, contact information, etc.), paying close attention to mandatory fields.
- Complete all SHRF-specific fields in the following sections: Identification; Expertise; Funding; and Contributions-Details.
- Choose the "Validate" tab on the top of your screen. Select SHRF from the drop-down list and then select Full CV or Abbreviated CV. **IMPORTANT:** Your printed CV must indicate that it is an "Official Copy", which confirms that it has been validated.
- Choose the "Print/Preview" tab at the top of your screen. Select SHRF from the drop-down list and then select Full CV.
- Print your CCV and append it to this application.
- **NOTE: Despite the fact that CCV requires applicants to attach a list of publications to their SHRF CCV, the attached document will not print out when you "validate and print" your SHRF CCV; it will need to be printed out separately and manually attached.**

If you experience any difficulties with the CCV or have any questions, please contact our office at (306) 975-1680, toll-free at 1-800 975-1699, or by e-mail at helpdesk@shrf.ca

9. FULL PROPOSAL REVIEW PROCESS

Proposals will be assessed and ranked by an expert scientific review panel according to the following criteria:

- Strength of principal investigator(s)
- Appropriate expertise on research team to undertake proposed activities
- Strength of plan to facilitate teamwork and communication across geographical boundaries, if appropriate
- Likelihood that necessary facilities, equipment, personnel, and other resources and infrastructure will be available and/or in place to support the team's work (including evidence of support from universities, health regions, and others key partners)
- Quality, thoroughness, and feasibility of the research plan, including ethical and safety considerations

- Fit of research plan with the Call for Proposal's intended purpose and stated requirements
- Strength of plans for knowledge translation
- Reasonableness of budget for the proposed goals and activities
- Budget compliance with expenditure guidelines in Call for Proposals

To be eligible for funding, applicants must be rated highly by SHRF's peer-review committee (i.e., 3.5 or higher on the standard five-point scale). All applicants will receive notification of their results by letter, along with reviewers' feedback.

10. TERMS AND CONDITIONS OF AWARD

10.1. Grant Disbursement and Expenditures

- Approval from a recognized research ethics review board will be required before funding is released for research activities.
- Operational approvals must be in place before funding for research activities is released, according to the research plan submitted to SHRF.
- The Principal Investigator(s) must agree to the terms and conditions of the grant by signing a Notice of Acceptance Form. In the case where there are two Principal Investigators, only one will be responsible for the overall financial administration of the grant.
- Grant funding will be authorized on a yearly basis, providing terms and conditions of the grant continue to be met.
- Spending shall be limited to yearly authorized amounts; SHRF will not be responsible for any spending over authorized amounts or for non-eligible expenses.
- Grant payments will be made to the principal investigator's home institution on a monthly basis according to usual SHRF procedures.
- If a portion of the research is occurring outside Saskatchewan, arrangements for the transfer or payment of research funds will be made with the Investigators' home institutions; this may be done according to existing transfer agreements between institutions or via a contract between SHRF and the institutions.
- SHRF will be responsible for disbursing and monitoring finances, which includes ensuring that all terms and conditions are met before funding is released, both initially and throughout the grant term, and that all ethical and operational approvals are in place before funding for research activity commences.
- Where subsequent stages of the overall study depend on the results of earlier stages, funding for each stage will be released only when predetermined conditions have been fulfilled and on advice from SHRF's MS Advisory Panel.

10.2. Grant Monitoring and Reporting

Monitoring of all ethical and operational approvals will be ongoing for the duration of the research project. Progress will be monitored generally by SHRF and the SHRF MS Advisory Panel through annual operational reports and financial statements of account. Items to be included in annual reports will include progress on key deliverables and milestones reached, money spent to date, identification of renewals or new approvals and permits, any changes in objectives, and identification of changes in research plans that might prevent the team from completing the study on time, or as intended. A final report will be required after project completion. Refer to SHRF's *Awards Guide* for more details on grant monitoring and accountability.

Additional reporting may be required at predetermined times based on milestones identified in the research proposal. Funding for subsequent stages is dependent on satisfactory reports which must be approved by SHRF's MS Advisory Panel.

A data safety monitoring board (DSMB) will receive reports and monitor study data on a regular basis to ensure the safety of study subjects.

11. FULL PROPOSAL SUBMISSION CHECKLIST

Proposal Format

- 12 point font (Times, Arial, or Calibri)
- 1 inch page margins
- PI's surname in top-right header
- Page numbers (X of Y) in bottom-right footer

Proposal Requirements

- Appendix A – Title Page
- Appendix B – Signature Page
- Research Description of no more than 25 pages (including Appendix C - Gantt Chart, images, figures, tables, and graphs)
- Appendix D – Budget and Justification
- References
- Letters of Support
- Common CVs of Research Team (not collaborators)
- Statements of potential or real conflicts of interest, if applicable

Proposal Copies

- Signed original
- 6 copies (including CVs and appended documents)
- Copy on CD (pdf format)

12. CONTACT

For more information please contact:

Trina Evitts, Funding Programs Advisor
Saskatchewan Health Research Foundation
253-111 Research Drive
Saskatoon, Saskatchewan, S7N 3R2
Phone: (306) 975-1680 or 1-800-976-1699 (toll-free)
Fax: (306) 975-1688
Email: tevitts@shrf.ca

APPENDIX A –Title Page Template

Funding Opportunity: Studying the Liberation Procedure for Multiple Sclerosis (MS)

Project Title:

Total Amount of Funding Requested:

Principal Investigator(s):

Name:

Affiliation:

Address:

Telephone:

Fax:

E-mail:

Administrative Assistant phone and email (if applicable):

Co-Investigator(s):

Name:

Affiliation:

Address:

Telephone:

Fax:

E-mail:

Administrative Assistant phone and email (if applicable):

APPENDIX B - Signature Page Template

1. Title of Project _____

2. Principal Investigator(s) _____

3. Signatures of Principal and Co-Investigators (add rows to table as necessary): The undersigned hereby: (1) agree that the information provided in this application is accurate, (2) accept the terms and conditions for research funding as outlined in the *SHRF Awards Guide* and the *Studying the Liberation Procedure for Multiple Sclerosis (MS) Call for Proposals*, (3) agree to disclose, now and as they arise, any potential or real personal or commercial conflicts of interest with the research process or outcome of this research, and (4) agree to ensure that research funded by SHRF will adhere to nationally accepted ethical, legal, and safety standards.

Name (please print)	Institution	Signature	dd/mm/yr	No personal financial benefit ¹	No commercial benefit ²
				<input type="checkbox"/>	<input type="checkbox"/>
				<input type="checkbox"/>	<input type="checkbox"/>
				<input type="checkbox"/>	<input type="checkbox"/>
				<input type="checkbox"/>	<input type="checkbox"/>
				<input type="checkbox"/>	<input type="checkbox"/>

¹ "Personal financial benefit" refers to potential personal financial benefit from the process or results of the proposed research. If a potential or real conflict exists, please append a letter of explanation with the application.

² "Commercial benefit" refers to the potential significant financial benefit of any company if this proposal is successful. If a potential or real conflict exists, please append a letter of explanation with the application.

4. Host Institution of Principal Investigator(s)

We, the undersigned, support this application for SHRF funding and accept the terms for research funding as outlined in the *SHRF Awards Guide* and the *Studying the Liberation Procedure on Multiple Sclerosis (MS) Call for Proposals* as well as any commitment of host institution resources referred to in this application.

Dean (or designate)	Dept. Head (or designate)	University Research Officer
Name	Name	Name
Signature	Signature	Signature
Date	Date	Date

Appendix C – Gantt Chart Template

Note: The milestones, deliverables, and shading below are for demonstration purposes only. Research teams will propose their own milestones and deliverable due dates.

		April - June 2011	July - Sept	Oct-Dec	Jan-March	April - June 2012	July - Sept	Oct-Dec	Jan-March	April - June 2013	July - Sept	Oct-Dec	Jan-March	April - June 2014	July - Sept	Oct-Dec	Jan-March	April - June 2015	July - Sept	Oct-Dec	Jan-March	
Milestone 1																						
	Deliverable 1.1	■	■	■																		
	Deliverable 1.2	■	■	■	■																	
	Deliverable 1.3					■	■	■	■													
Milestone 2																						
	Deliverable 2.1									■	■	■	■									
	Deliverable 2.2									■	■	■	■	■								
	Deliverable 2.3													■	■	■	■	■	■	■	■	■

APPENDIX D – Budget and Justification Template

Separate budget tables are required for each year of the project and for overall project expenses. For example, if the proposed project is a five-year project, six budget tables should be submitted – one for each year, and one for overall expenses.

Name of Principal Investigator(s):

Title of Project:

Year of Project – (e.g., Year 1)

	Total SHRF funds	Total Other funds ¹	Total
1. Salary and Stipend			
a. Research Staff			
b. Research trainees (e.g., graduate students, research fellows)			
c. Administrative support			
d. Health Services Providers			
e. Other salaries – please specify			
f. Time release for Investigators			
2. Equipment			
a. Purchase or rental			
b. Maintenance costs			
c. Operating costs			
d. Other operating costs			
3. Materials and Supplies			
4. Services			
4. Travel			
a. Research-related travel			
b. Team meetings			
c. Research participants			
d. Knowledge Exchange/Dissemination travel			
5. Other			
TOTAL OPERATING			

¹ A letter of support from each contributing partner certifying the cash commitment and/or in-kind contribution is required with submission of the proposal.

Budget Justification – Year XXXX

Provide justification for each line item in the requested budget. Be sure to provide details on the components that are funded through ‘Other’ contributions, whether cash or in-kind.

Name of Principal Investigator:

Title of Project:

Year of Project – (e.g., Year 1)

1. Salary and Stipend - List each position, specify names (if known), and describe their contributions to and involvement in the research, as well as the percentage of their time allotted to this project. List the pay rates of each position, including benefits (salary/stipends policies of the host institutions apply).

a. Graduate students

b. Postdoctoral Fellows

c. Technicians and professional assistants

d. Administrative support

e. Health Services Providers

f. Other salaries

2. Equipment - Provide details of purchase, maintenance, operating and other costs, where applicable. For equipment over \$20,000, provide a quote.

a. Purchase or rental

b. Maintenance costs

c. Operating costs

d. Other operating costs

3. Materials, Supplies– Provide details of materials, supplies.

4. Services – Provide details of services and technical contracts. (e.g., reimbursement for clinical care to hosting hospitals/clinics)

4. Travel – Provide details of eligible travel expenses.

a. Research related field trips

b. Team meetings/workshops

c. Conferences

d. Other Knowledge Exchange/Dissemination

5. Other – Provide details, where applicable.