SUPPLEMENTAL MATERIAL

Supplemental Methods

Supplemental Methods I: Development of interview guides

Topic guide development was informed by advice from MSC content experts (ML, DF, DD) to be appropriate for the specific behaviour and clinical context. To help clarify domain elements of interest (e.g. barriers to attending clinical trial follow-up appointments), we asked participants to draw from comparable past experiences (e.g. attending rehabilitation appointments). Four pilot interviews (two patient and two physiatrist) were completed to further refine the interview guides; minor modifications were suggested to improve clarity.
Supplemental Methods II: Semi-structured interview guide for identifying barriers and facilitators to implementing mesenchymal stromal cells (stem cells) as a therapy for chronic stroke – patient interview guide

Preamble

Thank you for agreeing to speak with me today. As we discussed, we are interested in what you know and think about receiving mesenchymal stromal cells, a type of adult stem cell, which might be useful for treating chronic stroke. Our discussion shouldn't take more than an hour (probably less). As discussed and if still ok with you, I will audio-record our discussion just to make sure that I capture all your thoughts so that I can listen back to them later.

All identifying information (your name or the names of others) that you mention will be removed from the interview transcripts; making this effectively anonymous. If you want to take a break or stop our discussion before I have asked all of the questions or if you wish to withdraw from the study you are completely free to do so. There may appear to be overlap between questions but each question is worded to obtain specific information and therefore you may find that answers are repeated. It is important to note that there are no right or wrong answers to the questions; we are simply interested in your views about receiving stem cells. Your responses will be anonymized so that no one will know what your specific answers were.

Any questions before we start?

We will refer to mesenchymal stromal cells as MSCs for simplicity during the interview. There is evidence from studies in the lab that MSCs, which are a type of stem cell that is found in tissues throughout the human body, have potential for treating chronic stroke. In addition to the
ability to help repair tissues, these cells might also be able to help to decrease inflammation in the brain through their interactions with the immune system. In the presence of tissue inflammation and injury, MSCs can produce substances that help reduce the damage and promote tissue healing. There have been very few studies using MSCs to treat stroke, so it’s difficult to say how exactly they may benefit your health. We are also only beginning to understand the potential benefits and risks that MSCs might have on the human body; however, the evidence so far is suggesting that they may be safe.

Within the next year, we plan on implementing a clinical trial of MSC therapy for stroke in Canada. This trial will be an “early” phase trial, in which the main goal is confirm that MSCs are safe. This will be the first time these cells have been tested in Canada in patients with chronic stroke. Before we run that study, we wanted to better understand the views of people who might ultimately be invited to participate. Just to clarify: you may never be asked to participate in the stem cell study yourself; instead, we are hoping to get views about receiving stem cells so that we can plan our study appropriately for the patients who do receive them. And if anything isn’t clear, don’t be shy to ask me to clarify.

All ok so far? Any questions?

To begin with, for the whole of the rest of our discussion, I’d like you think about the hypothetical situation as it might apply to you if you were in that situation: enrolling and participating in a clinical trial of stem cells to treat your chronic stroke.

Background Questions

1. What year were you born?

2. When did you have your stroke?
3. Thinking about your own experiences, what might affect whether you would decide to enroll in this clinical trial? (Prompts: Have you ever been in a clinical trial yourself? (If yes) How did that go? Remind about randomization, how might the idea of being placed into a “no treatment” group affect your decision?)

4. If you were participating in a clinical trial, how often might something else be more urgent than attending a follow-up appointment? (Prompts: How many is too many (Frequency)? What length of appointment would be appropriate for one follow up appointment? Follow-up duration: 1 year? 2 years? 5 years?)

Knowledge (1):

1. Can you tell me about what you know about stem cells? Have you heard about them? Do you know how they are collected? What do you think about that?

2. What do you know about clinical trials? (If they don’t know, explain the phases and which phase this trial would be) (Prompt: Describe the process of randomization, control group (emphasize that they will still receive standard care in control) describe that this trial is a safety (phase I/II) trial and what that entails)

3. What information would you need to feel comfortable participating in a trial of stem cells for chronic stroke? From who would you like to receive that information?

Skills (2):

4. If you heard about an available clinical trial of stem cells, how would you go about enrolling or participating?

5. What are the specific skills and techniques that you would use to enroll and participate in this stem cell trial?
Social/Professional Role and Identity (3)

6. How would receiving stem cells as part of this trial fit with how you see yourself as a person and what is important to you? (Prompt: any moral/ethical issues?)

Beliefs about Capabilities (4)

7. How confident are you that you could participate in a trial of stem cells for chronic stroke? What might make you feel less confident that you could? (Prompts: Any moral/ethical issues? Would that change based on if the cells were injected into your brain or if applied through an IV? How?)

Optimism (5):

8. Do you expect that participating in a trial of stem cells for chronic stroke will result in more good things than bad things for yourself? In what way?

Beliefs about Consequences (6):

9. What are some of the benefits that you see in participating in this clinical trial? (Prompt: For you, for future patients, research)

10. And what are some of potential negative aspects that you see of participating in this clinical trial? (Prompt: For you, for future patients, for anyone else)

Intention (8):

11. How motivated would you be to participate in a trial of stem cells if its goal was to test the safety of stem cells, but not to test if it improved your health as a primary goal? (Prompt: How would the possibility of a placebo control affect your motivation?)

12. Would you participate in a trial of stem cells for chronic stroke if one is available in the next year? (Prompt: If yes, why? If no, why not?)
Goals (9):

13. What would you like to achieve by participating in a trial of stem cells? (*Prompts: Symptom reduction, ADL improvement, personal achievement*)

14. What would motivate you to participate in a trial of stem cells for chronic stroke? (*Prompts: Health benefits, altruism/making a difference? Would that change based on if the cells were injected into your brain or if applied through an IV? How?*)

Memory, Attention, and Decision Processes (10):

15. Generally, in your ongoing rehab, how often might something else be more urgent than visiting your therapist? (*Prompt: Have you ever forgotten a rehab appointment? What things are more urgent?*)

16. How often would you say you might forget a follow-up appointment throughout the course of a trial?

Environmental Context & Resources (11):

17. What resources do you need to be made available to you in order to participate in a trial of stem cells? (*Prompts: Transportation/parking, financial, caregiver, childcare? What tools?*)

Social Influences (12):

18. Can you rely on the health system to support you when things get tough if you participated in a trial of MSC therapy for stroke? (*Prompts: “Things get tough”, health (mental/physical]*)

19. Whose opinion is important to you when considering whether to participate in a stem cell trial for chronic stroke? (*Prompts: Other patients, family members, caregiver, physician, nurse? Who would influence your decision most?*)
Emotion (13):

20. When you imagine participating in stem cell trial, what emotions come to mind? *(Prompts: Guilt, worry, satisfaction, inspired, nervous, stressed, happy, sad?) Would this change if the cells were administered through a direct injection into your brain or through an IV line? How? How would these emotions influence whether you wish to participate in the stem cell trial?*

Behavioural Regulation (14):

21. What strategies would you have in place for keeping track of appointments during the trial, such as follow-ups? And for attending the appointments? *(Prompts: What can you do specifically? (Not the clinic or anyone else) Is there anything specific that you already do that helps you keep track of appointments and follow-ups?)*

Other:

22. Thinking about everything that you mentioned that might impact on your decision to participate in a stem cell trial, what would you say is the most important factor that would influence your decision?

23. Is there anything else that is a barrier to you participating in a trial on MSC as a therapy?

*Any final thoughts?*

*Thanks so much for your time!*
Supplemental Methods III: Semi-structured interview guide for identifying barriers and facilitators to implementing mesenchymal stromal cells (stem cells) as a therapy for chronic stroke – physician interview guide

Preamble

Thank you for agreeing to speak with me today about your thoughts and views about using mesenchymal stromal cells, a type of adult stem cell, which may be useful chronic stroke treatment. This should take approximately thirty minutes and will be audio-recorded to ensure that all key points are accurately documented. Any identifying information (for example your name or the names of other individuals) that you use in the course of our discussion will be removed from the interview transcripts. If you want to end our discussion before I have asked all of the questions or if you want to withdraw from the study you are free to do so at any point. There may appear to be overlap between questions but each question is worded to obtain specific information and therefore you may find that answers are repeated. It is important to note that this is not a test and there are no right or wrong answers to the questions; rather, we are simply interested in your views about giving MSCs so that we can appropriately plan our future research in this area. Your responses will be anonymized so that no one will know what your specific answers were.

Any questions before we start?

We will refer to mesenchymal stromal cells as MSCs for simplicity during the interview. There is evidence from animal models of stroke that MSCs, a type of stem cell that is found in bone marrow, adipose tissue, and umbilical cords have potential for treating chronic stroke. In addition to their cytoprotective factors, these cells might also decrease tissue inflammation in the brain.
There have been few studies using MSCs to treat stroke, so the exact benefits are still unknown. We are also only beginning to understand the exact safety profile of these cells; however the evidence so far is suggesting that they may be safe. Within the next year, we plan on implementing a clinical trial of MSC therapy for stroke in Canada. This trial will be a phase 1/2 trial and will be the first time these cells have been tested in Canada in patients with chronic stroke.

While the exact design of the trial is yet to be established, it is likely that the physicians in the trial will be required to help screen patients and provide ongoing care. This will include conducting follow-up appointments for a minimum of a year, and could extend further and involve performing functional outcome measures. Prior to conducting a clinical trial with patients to examine the safety and effectiveness of MSCs for chronic stroke we are interested in your views about giving MSCs as a potential treatment.

In relation to that, I would like you to think of the following specific activity: You personally screening patients with chronic stroke for participation in a clinical trial of MSC therapy in the next month and providing ongoing care after they have had the procedure.

Demographic and background questions:

1. So to begin, how long have you been a physiatrist?
2. Could you tell me what your role is with respect to the care of patients with stroke?
3. What proportion of patients in your current clinical practice have chronic stroke?
4. Thinking about your own experiences, what might be some reasons that you would not be able to screen patients for a clinical trial?
5. Tell me about your past experience screening patients for a clinical trial. (Prompts: Have you screened patients for trials in the past? (If yes) How did that go? Have you ever received training to screen patients for a clinical trial as a clinician? What sort of training...
would you need? Have you ever performed functional outcome tests? (Ex. NIHSS, mRS, BI, ADL)

6. With regards to follow-up appointments, what frequency seems reasonable? (Prompt: Duration of follow-up appointments, duration of follow-up)

Knowledge (1):

1. What do you know about MSCs in general, and for chronic stroke in particular? (Prompts: Have you ever heard about MSCs for stroke? Have any of your patients asked you about stem cell therapy?)

Social and Professional Role and Identity (3):

2. How do you see screening for this trial in relation to your role as a clinician? (Prompts: Do you see this as something that is a part of your current role? Do you think it should be part of your role? (If no) Whose role should it be? What would be your responsibilities in this position?)

Belief about Capabilities (4):

3. You mentioned a few reasons that might stop you from being able to screen patients for a clinical trial. How confident are you that you could screen patients for a trial of MSCs? (Prompts: What might make you feel more confident? What might make you feel less confident?)

4. Do you feel comfortable performing functional outcome tests as part of a follow-up appointment?

Skills (2):

5. What are the specific techniques or skills that you need to screen for enrolment for this trial?
Intention (8):

6. Would you screen your patients as part of a trial of MSCs for clinical stroke if one is available in the next year? (Prompt: Why or why not?)

7. How motivated would you be to screen patients for a trial of MSCs if its goal was to test the safety of MSCs, but not to test if it improved your patients’ health?

8. What would motivate you to agree to screen patients for a trial of MSCs for chronic stroke? (Prompts: Patient benefit, science benefit, clinical care)

Beliefs about Consequences (5):

9. Do you expect that a trial with MSCs for chronic stroke will result in more good things or bad things for the patients you screen? (Prompt: In what way?)

10. What are some of the benefits that you see of screening patients for a trial of MSCs for chronic stroke? (Prompts: For you, for your patients, for anyone else)

11. What are some of the disadvantages that you see of screening patients for a trial of MSCs for chronic stroke? (Prompts: For you, for your patients, for anyone else)

12. What do you think your patients will achieve if they were to receive MSCs? (Prompts: Symptom reduction, ADL improvement, personal achievements)

13. How would providing ongoing care for patients during the trial benefit you? (Prompts: Your patients, possible disadvantages)

Goals (9):

14. Generally, in your clinical practice, how often might something else be a higher priority than screening for a clinical trial? (Prompts: Might something be more urgent than providing ongoing care? How do you think this will impact your ability to screen?)
Memory, Attention, and Decision Processes (10):

15. Do you think it is likely that you might sometimes forget to screen for this trial? When would you most likely forget? What might help?

Environmental Context and Resources (11):

16. What resources do you need to be made available to you in order to participate in a trial of MSCs for chronic stroke? What resources do you already have? *(Prompts: Training (for screening vs ongoing care), institutional support? What tools?)*

Social Influences (12):

17. Who else’s views might have an impact on whether you decide to screen patients for this trial, and whether you screen them? *(Prompts: Patients, their family, other physicians, colleagues, your family (time))*

Emotion (13):

18. Would screening add any level of stress to your current workload? *(Prompts: How would that stress influence screening for this trial? (ie. Make reluctant, not want to get involved, etc.))*

Behavioural Regulation (14):

19. What are some strategies you might use to stay on top of screening patients and providing ongoing care? *(Prompts: What can you do personally to help stay on top of screening patients and provide ongoing care? (Not the clinic/anyone else) Is there anything in the past that has helped you stay on top of screening patients and provide ongoing care?)*

Other:

20. Based on what we have discussed, what would you say is the most important factor influencing your decision to screen for a trial of MSCs for chronic stroke?
21. What would be the most important factor influencing your decision to provide ongoing care?

22. Do you see anything else as being a barrier to screening patients for this clinical trial?

*Any final thoughts? Thanks so much for your time!*
## Supplemental Tables

Table I. Summary of belief statements and sample quotes from patients assigned to domains identified as not relevant

<table>
<thead>
<tr>
<th>Domain</th>
<th>Specific Belief</th>
<th>Frequency (n=13)</th>
<th>Sample Quote</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reinforcement</td>
<td>None identified</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Memory, Attention and Decision Processes</strong></td>
<td>I do not think it's likely that I will forget an appointment for the trial.</td>
<td>12 (92%)</td>
<td>“I don't forget any appointments.” (P7)</td>
</tr>
<tr>
<td></td>
<td>I may forget about appointments for this trial.</td>
<td>1 (8%)</td>
<td>“I forget quite often right now.” (P2)</td>
</tr>
<tr>
<td></td>
<td>My condition at the time of enrolment would factor into my decision to participate.</td>
<td>1 (8%)</td>
<td>“Yeah my condition, yeah. If I’m all better I wouldn’t participate in it as much as if I really want to get better, I feel like I would do it more so. Like it really depends on my condition.” (P13)</td>
</tr>
<tr>
<td></td>
<td>I would weigh the pros and cons when deciding whether to participate.</td>
<td>1 (8%)</td>
<td>“… It’s just like if the pros outweighs the cons, you just kind of have to kind of evaluate it by yourself if you’re willing to put yourself out there. But for me that’s what I would do…” (P13)</td>
</tr>
<tr>
<td>Behavioural Regulation</td>
<td>I have strategies in place to help me participate in this trial.</td>
<td>11 (85%)</td>
<td>“I would use the daily planner.” (P2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>“I put everything in my phone. In my phone calendar.” (P5)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>“Not uh well other than pencil and paper you know.” (P9)</td>
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</table>
Table II. Summary of belief statements and sample quotes from physicians assigned to domains identified as not relevant

<table>
<thead>
<tr>
<th>Domain</th>
<th>Specific Belief</th>
<th>Frequency (n=13)</th>
<th>Sample Quote</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reinforcement</td>
<td>I have had a negative experience with a clinical trial in the past.</td>
<td>2 (15%)</td>
<td>“We are running a research project on falls risk in the inpatient unit and it sounds very simple, but we encountered so many barriers and difficulties along the way. I think overall the clinical research trial implementation in inpatient stroke would have many barriers that we can’t even predict right now.” (P4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>“We have walked away from studies before because there’s too much burden on the subject.” (P5)</td>
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</tbody>
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