So You Want to Give Stem Cells to Babies? Neonatologists and Parents' Views to Optimize Clinical Trials

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Objective To identify barriers and enablers that may influence parents' and neonatologists' participation in clinical trials of mesenchymal stromal cells for bronchopulmonary dysplasia.

Study design This qualitative study involved one-on-one semistructured interviews with parents of extremely preterm infants (n = 18) and neonatologists (n = 16). Interview guides and directed content analysis were framed using the theoretical domains framework, a tool specifically developed for implementation research to identify influences on behavior.

Results Key barriers for parents included their lack of knowledge about clinical trial processes in general, stem cells, and concerns about their risks and side effects. Importantly, parents preferred to be approached for recruitment directly by a neonatologist, either before delivery or 1 or 2 weeks after birth. However, the majority of neonatologists felt that approaching parents was not part of their role. Neonatologists reported competing priorities, time commitment, costs, and lack of institutional support as significant barriers to their ability to recruit patients.

Conclusions By integrating stakeholders early into the development of a clinical trial of mesenchymal stromal cell therapy, we identified and can address important barriers to enrollment. Some identified barriers were unanticipated and could have compromised recruitment had they not been identified by this study. We suggest that this approach can be used more broadly for other early phase clinical trials in pediatrics. *(J Pediatr 2019;210:41-7)*.

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Preterm birth is a leading cause of infant morbidity and mortality worldwide.[1] Bronchopulmonary dysplasia (BPD), a chronic lung disease with potential life-long consequences, remains one of the most prevalent complications.[2] Survivors with BPD have impaired respiratory function, increased hospital readmission rates, and exhibit more neurodevelopmental problems.[3,4] Currently, there is no treatment to prevent or ameliorate BPD.[5]

Numerous preclinical studies support the role of cell therapy, specifically mesenchymal stromal cells (MSCs), in promoting lung repair and lung growth in part owing to their pleiotropic effects.[6] A systematic review and meta-analysis of MSCs in experimental neonatal lung injury models in rodents provides strong evidence for the therapeutic potential of this cell therapy in BPD.[7]

Of particular concern in cell therapy trials is the failure to enroll patients within anticipated time periods.[8] Low recruitment rates remain a major threat to trial feasibility and can be traced to failing to engage stakeholders early in the translation process.[8,9] Before considering an early phase trial of MSC therapy for BPD, potential barriers to such a trial must be addressed.

The existing evidence base around the barriers and enablers to trial participation focuses predominantly on later phase trials.[10-12] Little is known about which factors act as barriers or facilitators in early phase cell therapy trials in adult patients and nothing is known in neonates.[13] A parent's decision to consent to a novel trial of an experimental therapy on behalf of their extremely preterm child is complex and influenced by multiple factors. Furthermore, a clinician's recruitment of patients to an MSC trial likely depends on a range of factors. Understanding these factors in a structured manner may help to ensure that any barriers are identified sufficiently early to ensure that they can be addressed

BPD	Bronchopulmonary dysplasia
MSC	Mesenchymal stromal cell
TDF	Theoretical domains framework

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B.T. is supported by the Ontario Institute of Regenerative Medicine, Canadian Institutes of Health Research (grant# 143316) and holds the University of Ottawa Partnership Research Chair in Regenerative Medicine. M.L. is supported by The Ottawa Hospital Anesthesia Alternate Funds Association and the Scholarship Protected Time Program, Department of Anesthesiology and Pain Medicine, University of Ottawa. The authors declare no conflicts of interest.

Portions of this study were presented as an abstract at the Canadian National Perinatal Research Meeting, February 14, 2018, Banff, Canada; and the Till and McCulloch Meetings, November 12-14, 2018, Ottawa, Canada.

https://doi.org/10.1016/j.jpeds.2019.03.005

before trial launch and promote recruitment, retention, and successful trial completion.

Much of the existing literature on barriers and enablers to trial participation focuses either on recruiters or participants (rarely both) and lacks a comprehensive approach. The Theoretical Domains Framework (TDF)[14,15] is based on a synthesis of key factors known to impact behavior, which can be used to inform qualitative interviews and provide a systematic approach to address barriers in implementation research. The TDF includes 14 domains that describe factors that may act as barriers and enablers to a given behavior. The TDF has been used across several health care systems[15] and across a range of clinical settings, but never in neonatology.[16-19] Our study aimed to apply the TDF to identify the barriers and enablers that may influence participation in (parents) and recruitment to (neonatologists) a planned MSC trial.

Methods

The study was approved by the Ottawa Health Science Network Research Ethics Board and The Children's Hospital of Eastern Ontario (CHEO) Research Ethics Board (Protocol number: 20170051-01H, 16/177X).

We recruited both parents and neonatologists to this study. We invited Canadian neonatologists working in academic teaching programs identified through the Canadian Neonatal Network. We asked each participating neonatologist to identify additional neonatologists working in their center (snowball sampling) for interviews who may offer differing views (**Figure**; available at www.jpeds.com). A nonmedically trained researcher was selected to conduct interviews with neonatologists to promote greater detail of explanation of barriers that may otherwise have been implicit, and to ensure that responding neonatologists could feel more open to confidentially discuss barriers with someone outside of their professional network. Consistent with inclusion criteria for the planned trial, we recruited parents of preterm infants born at <28 weeks of gestation at a tertiary care neonatal intensive care unit in Ontario, Canada (**Figure**). To ensure that any clinical concerns raised from the parents would be appropriately addressed, the interviews were conducted by a physician trained in conducting interviews using the TDF. The interviews were conducted either in person or by telephone. Interviews were digitally recorded, transcribed, and de-identified before qualitative data analysis.

The behaviors of interest were participation in (parents) and recruitment to (neonatologists) a planned MSC trial for BPD (**Appendix 1**; available at www.jpeds.com). Two semistructured interview guides (one for the parents, one for the neonatologists) were developed based on the 14 domains of the TDF, with open-ended questions. The definitions of the 14 TDF domains and examples of related interview questions are described in **Table I**. The guides were developed in collaboration with a health psychologist, a research nurse, the parents of an extremely preterm infant, and 2 neonatologists. The complete interview guides can be found in **Appendix 2** and **Appendix 3** (available at www.jpeds.com).

Data Analyses

We used data saturation guidance from Francis et al to ensure an adequate sample size to reach thematic saturation.[20] Data saturation is achieved when no new concepts (or belief statements) emerge from 3 consecutive interviews after an established minimum initial sample size of 10. If new concepts are raised, interviews should proceed until 3 consecutive interviews do not raise any new themes. The de-identified interviews were analyzed using NVivo 11 (QSR International Pty Ltd, Version 11). The analysis involved the following 3 steps consistent with standard recommendations for TDF-based qualitative studies[21]: (1) coding, which represents the analysis of participants' responses with categorization to ≥1 domains, (2) generation of specific belief statements, which is created by grouping a set of responses reported by different participants with similar underlying ideas and/or beliefs, and (3) identification of key theoretical domains. Detailed data analysis methods can be found in **Appendix 4** (available at www.jpeds.com).

Results

Interviews were conducted between August 2017 and February 2018; 18 parents and 16 neonatologists working in 9 tertiary neonatal intensive care units across Canada participated in interviews. Interviews lasted between 21 and 52 minutes (mean, 33.6 minutes) for neonatologists and between 24 and 100 minutes (mean, 43.1 minutes) for parents. Participant characteristics are described in **Table II**.

Interviews with parents

Key themes from interviews with parents were identified within 6 relevant domains (**Table III**). The majority of parents reported having little knowledge regarding clinical trial processes in general (n = 12) or for stem cell therapy specifically (n = 15). They did, however, express a keen interest in learning more about stem cell therapy, the potential benefits and risks, and past study outcomes. For many, knowing more about the benefits, risks, and outcomes was critical to deciding whether they would participate in the trial (TDF domains: knowledge, beliefs about consequences, intention).

Parents also discussed wanting detailed information regarding stem cell therapy procedures and the proposed clinical trial and mentioned the importance of delivering this information in lay language, translated into parents' preferred language. With regard to communication strategies, the parents valued a combination of a one-on-one discussion with a health care provider along with tangible information provided through written documentation, a

Table I. Theoretical domains framework definitions and associated questions

TDF domains	Definitions (Cane et al, 2012[15])	Example interview questions for parents or neonatologists
Knowledge	An awareness of the existence of something	Parent: Have you ever heard about stem cells?
Skills	An ability or proficiency acquired through practice	Neonatologist: What are the specific techniques or skills that you need to identify potential patients for enrollment for this trial?
Social/professional role and identity	A coherent set of behaviors and displayed personal qualities of an individual in a social or work setting	Neonatologist: Do you think that the neonatologists should be involved in the consenting process of a new intervention, like MSCs trial?
Beliefs about capabilities	Acceptance of the truth, reality, or validity about an ability, talent, or facility that a person can put to constructive use	Neonatologist: How confident are you that you could identify preterm babies on your unit for a potential trial of MSCs for BPD?
Optimism	The confidence that things will happen for the best or that desired goals will be attained	Parent: Do you think that overall the good aspects outweigh the bad with regards to enrolling your child in this trial? In what way?
Beliefs about consequences	Acceptance of the truth, reality, or validity about outcomes of a behavior in a given situation	Neonatologist: What are some of the benefits that you see of identifying patients for a trial of MSCs for BPD?
Reinforcement	Increasing the probability of a response by arranging a dependent relationship, or contingency, between the response and a given stimulus	Neonatologist: What would motivate you to regularly and routinely identify patients for a trial of MSCs for BPD?
Intentions	Conscious decision to perform a behavior or a resolve to act in a certain way	Neonatologist: Would you identify potential patients as part of a trial of MSCs for BPD? Why or why not?
Goals	Mental representations of outcomes or end states that an individual wants to achieve	Parent: What are some of the things you would want to achieve by enrolling your child in this trial?
Memory, attention, and decision processes	Ability to retain information, focus selectively on aspects of the environment, and choose between 2 or more alternatives	Neonatologist: Do you think that it is likely that you might sometimes forget to identify potential patients for this trial?
Environmental context and resources	Any circumstance of a person's situation or environment that discourages or encourages the development of skills and abilities, independence, social competence, an adaptive behavior	Parent: What would be the best timing to approach you and discuss about this study?
Social influences	Interpersonal processes that can cause individuals to change their thoughts, feelings, or behaviors	Parent: Who would influence your decision the most (in regards to considering whether to enroll you child or not)?
Emotions	Complex reaction pattern, involving experiential, behavioral, and physiological elements, by which the individual attempts to deal with a personally significant matter or event	Parent: If your child were to start participating in this clinical trial, how would you feel?
Behavioral regulation	Anything aimed at managing or changing objectively observed measured actions	Neonatologist: What are some strategies you would use to stay on top of identifying potential patients for this trial?

website or videos (domains: knowledge, environment, behavioral regulation).

Parents expressed a strong preference for receiving information from neonatologists, who were identified as key influential persons by the majority of participants (n = 12). Participants generally valued the input from knowledgeable persons and experts (n = 12) and many indicated they were influenced by family (n = 8). Participants discussed trusting and deferring to physicians' knowledge and expertise (domain: social influence).

When asked when would be best for researchers to approach parents about participating in the proposed clinical trial, participants were divided between preferring an approach before delivery (n = 9) vs 1 or 2 weeks after the delivery (n = 7). The consensus was the first week was not a good time because many felt overwhelmed and unable to decide regarding study participation (domains: environment, emotion).

Parents reported wanting and expecting a variety of physical health outcomes for their children if they were to receive stem cell therapy. They also voiced concerns regarding the risk of side effects and the potential for pain and harm. Despite their concerns, parents had predominantly positive views regarding the research process. Almost all (n = 15) said they would enroll their child in the clinical trial if it was offered to them, despite being made aware of the potential risks associated with stem cells administration (domains: beliefs about consequences, intention).

Interviews with neonatologists

We identified 6 relevant domains reflecting potential barriers and enablers for neonatologists' recruitment to the trial (**Table IV**). The majority of neonatologists interviewed (n = 12 of 16) knew about stem cells and their application for BPD. However, to contribute to recruiting for an MSC trial, they wanted to know more about results of preclinical studies and available evidence to date (n = 9). They were also aware of the steps they would take to identify or screen patients for a clinical trial of stem cells in BPD (n = 9). The need for clarity around study criteria and treatment administration was underlined by the majority of the neonatologists (n = 12; domain: knowledge).

In general, neonatologists had positive perceptions of what MSCs could offer for BPD. The perceived benefits included improved lung function, a reduction in long-term complications, and benefits for future patients. More than one-half

Table II. Characteristics of participants

Variables	Parents (n = 18)	Neonatologists (n = 16)
Male sex	5 (28)	10 (63)
Age of parent, y		
≤25	2 (11)	-
26-30	5 (28)	-
31-35	5 (28)	-
36-40	4 (22)	-
>40	2 (11)	-
Race/ethnicity		
White	13 (72)	-
Black	4 (22)	-
Other	1 (6)	-
Gestational age of preterm infant, weeks		
22	1 (6)	-
23	5 (28)	-
24	0	-
25	1 (6)	-
26	3 (17)	-
27	6 (33)	-
28	2 (11)	-
Familial annual income, before taxes, Canadian Dollar		
<25 000	7 (39)	-
25 000-<50 000	1 (6)	-
50 000-<75 000	0	-
75 000-<100 000	4 (22)	-
100 000-<150 000	1 (6)	-
≥150 000	5 (28)	-
Education level		
Less than high school	1 (6)	-
High school	8 (44)	-
College/university	9 (50)	-
Location of medical practice		
British Columbia	-	2 (13)
Alberta	-	1 (6)
Saskatchewan	-	1 (6)
Manitoba	-	1 (6)
Ontario	-	3 (19)
Quebec	-	4 (25)
New Brunswick	-	1 (6)
Nova Scotia	-	1 (6)
Years in neonatology practice		
<5	-	3 (19)
5-10	-	4 (25)
11-15	-	3 (19)
16-20	-	2 (13)
≥21	-	4 (25)

Values are number (%).

(n = 9) mentioned having limited knowledge about the safety data and long-term outcomes. Some raised concerns about the safety of using a blood product (n = 2) and the potential complications associated with the treatment administration (n = 2). Some misconceptions regarding stem cells and the way they are collected, stored, and administered were also reported (domains: beliefs about consequences, knowledge).

Most neonatologists (n = 12) were willing to participate in the screening or identification of patients for the trial (domain: intention). For some (n = 7), their participation and willingness to recruit could be influenced by the baby's stability (eg, reluctant to approach parents in case of acute clinical deterioration) and gestational age (eg, hesitant to recruit a less premature patient given the lower risk for developing severe BPD). Many mentioned that their participation may compete with other priorities such as clinical work (domain: goals). It was generally felt (n = 11) that identifying or screening patients was not part of their role as neonatologists (domain: social professional role and identity), although some neonatologists (n = 4) mentioned that they should be responsible for identifying and screening patients. The importance of a dedicated research team, along with institutional and financial support, was also reported as strong enabler (domain: environment). Indeed, the time commitment and cost associated with a trial were reported as important barriers to their participation.

Discussion

This study used the TDF to identify potential barriers and enablers that may influence parents' decision to enroll their infant in an MSC trial and neonatologists' ability to screen or identify patients. For each group, 6 theoretical domains were identified as relevant to describing barriers and enablers. These domains will directly inform the design of an upcoming clinical trial.

In an era where bench-to-bedside translation is extremely slow and only a small proportion of high-impact preclinical therapies are successfully translated into clinical practice, it is essential to understand and address clinicians' and patients' views and concerns. This study used the TDF to inform the planning of a clinical trial from the perspective of both those tasked with recruiting and those who provide consent. We identified specific factors that may not otherwise have been considered in the development of the trial and could have led to translational failure. The list of possible barriers and enablers (Table III and Table IV) provides a basis for optimizing trial procedures. These factors included barriers and enablers that aligned between parents and neonatologists, as well as factors that did not align between both that in particular can help to shape strategies for optimizing trial delivery. The factors also included misconceptions and ambiguities that can be corrected and resource needs and concerns that can be addressed. Thus, in addition to its specific usefulness for this particular trial, our findings may have broader usefulness to inform the planning of other trials or interventions in the neonatal intensive care unit.

One significant finding is that, although neonatologists felt that approaching families was not part of their role, the parents expressed that the physician was the key influential person in their decision to enroll their baby or not. This discrepancy raises questions regarding who is the most appropriate person to interact with families for trial recruitment. A combination of a well-trained research team and a knowledgeable physician may be the ideal solution to improve recruitment processes. Moreover, we learned through our interviews that we should avoid approaching families in the first week of life, because most of them felt overwhelmed and unable to decide regarding study participation during this period. We suggest that approaching

Table III. Summary of relevant barriers and enablers from interviews with parents

TDF domains	Specific beliefs	Sample quote	Frequency (out of 18)
Knowledge	I do not know much about clinical trials and stem cells.	"I know it's mostly studies done to determine if healthy medication is used for a cure. There are other things, but that's just a little bit that I know. I don't know much." (Parent – 13)	15
	I want to learn more about stem cell, potential benefits, risk and outcomes.	"I might also have more detailed questions about kind of like how are they programmed? So how are you getting these stem cells to them be lung cells." (Parent – 2)	15
Environmental context and resources	It is important to have access to comprehensive information.	"And don't use medical terms. We are profane… Maybe talk more on our level." (Parent – 6)	18
	The best time to approach me is before delivery or 1 to 2 weeks after.	"The first week was just like crazy and then especially having a C-section you're still in pain, you're doing this, you're trying to adapt. So I would definitely, if you can, not in the first week." (Parent – 11)	Before (n = 9), 1-2 weeks after (n = 7)
Behavioral Regulation	I suggest using different communication strategies to understand the clinical trial.	"Probably something like that and I would say a website as well so you can look at it and maybe a little more information because giving out a pamphlet might not be realistic because it could be like 50 pages." (Parent – 17)	14
Beliefs about consequences	I expect positive outcomes after MSC treatment.	"I know it's going to help their lungs." (Parent – 6)	16
	I have concerns about the potential risks associated with MSC treatment.	"Even if everything works well you still have concerns for later because when you have something natural and you add foreign cells, you don't know what that is going to create. Will it work?" (Parent – 10)	17
Intention	If that study was available now, I would participate.	"Your child is there, is not doing well, intubated and this option is offered to you, you know, I think that you take it. You jump on the opportunity for sure. Because you have no other options provided to you." (Parent – 15)	15
	If that study was available now, I would unsure about my participation.	"So I'm in the maybe now. It's just like okay, should I or should I not?" (Parent– 13)	2
	If that study was available now, I would not participate.	"I would definitely be more reluctant and I would have a lot more questions. It would take more to persuade me." (Parent – 2)	1
Social influences	The doctor is the key influential person.	"A doctor who works in the field and who gives me convincing answers, then I will be on board." (Parent – 7)	12
	My partner, family or support group will influence my decision.	"I would talk to the father of the baby for sure and if he would be not okay with it, whether it's logical or not, I would not do it because he's also the parent of my baby." (Parent – 3)	8

parents during the first week of life should be avoided when possible. Also, considering the important influence of family members on the parent's decision to enroll or not their baby, we also propose that a family member should be present for discussions around recruitment.

Another important, although not entirely surprising, finding concerned the domains of knowledge and beliefs about consequences voiced by both neonatologists and parents. For the parents, there is a need for detailed information that directly addresses the process and steps of a clinical trial, information about MSCs and their evidence base, as well as clarity on the short- and long-term consequences of MSC therapy. This information should be provided in lay language, using multiple delivery modalities that will be comprehended by people with diverse backgrounds and socioeconomic status. For the neonatologists, the need is for information on the most recent evidence around stem cells. This finding represents a potential target for optimizing trial recruitment processes, such as the development of an app, website, and/or video, that both physicians and parents could refer to and find relevant and appropriate information about the trial. However, disseminating clinical practice guidelines and other evidence to clinicians is not sufficient for ensuring practice change.[22] Other potential barriers such as competing trials and lack of role clarity may hinder even the most evidence-informed neonatologist.

Also, the overall positive perception in regard to what MSCs could do for preterm at risk of severe BPD was striking. These preterm patients, at risk of severe BPD, could potentially be identified early with clinical information integrated in a BPD predictor tool, such as the National Institute of Child Health and Human Development BPD outcome estimator tool.[23] Both groups were enthusiastic and eager to participate. This stakeholder engagement before the actual translation to bedside is reassuring from an anticipated enrolment perspective.

Table IV. Summary of relevant barriers and enablers from interviews with neonatologists

TDF domains	Specific beliefs describing barriers and enablers	Sample quote	Frequency (out of 16)
Knowledge	I know about MSCs and their use in BPD.	"I know that these cells are pluripotential and that they have been looked at in animal models. We have looked as a treatment for bronchopulmonary dysplasia." (Neonatologist – 7)	12
	I do not know much about MSCs.	"I've heard about stem cells and the promise that they show for regeneration of disease tissue. But specifically for BPD, I was not aware of that." (Neonatologist – 10)	4
	I know the steps I would take to identify or screen patients.	"We have a research assistant who basically selects all the babies less than a certain weight or a certain gestational age and will daily collect that information and then when a patient meets the eligibility criteria we try to approach the family as early as possible. And in order to approach the family we get the approval of the neonatologist who is on service taking care of that patient." (Neonatologist – 14)	9
	I need clear inclusion criteria and protocol.	"We need clarity about the criteria that would qualify a baby into the study, inclusion criteria, and exclusion criteria. So we need to have that very clear. Age and what the trajectory of the study is, so we're going to be recruiting during this time. We're going to be giving so many doses. The basic elements of the study, I think, are important." (Neonatologist – 1)	12
Environmental context and resources	I need leadership and team onboard for screening to proceed.	"We have a neonatal research team which is part of our neonatal intensive care unit and we make all the decisions together. When we decide to go through any research, we prepare our team for that research." (Neonatologist – 15)	6
	I need financial support available.	"We would need financial support. I can tell you we've tried to do research here without using a clinical research unit for a study such as this and it just doesn't work. If you can't hire one of them, you just don't get the same enrolment than if you actually do it the other way." (Neonatologist – 7)	6
Beliefs about consequences	I believe there are a lot of benefits associated with MSCs administration.	"The biggest benefit is I believe that these are going to work. That's number one. So I think the biggest benefit is that it'll actually be good for our patients." (Neonatologist – 7)	6
	I do not know enough about the safety data and long-term outcomes.	"Well we don't know the long term effects, so we can't reassure patients with a great deal of reassurance because we don't know. I mean things may happen in animal studies, but they may happen quite differently in human studies." (Neonatologist – 4)	9
	It is expensive and time costly to facilitate the trial.	"I think that it takes up a lot of time to conduct the studies, not just for the main investigator, but for the site investigators as well. So it takes a great deal of time. Sometimes, depending on the study, with not very much kind of gain either academically or in terms of funding." (Neonatologist – 4)	4
	I believe some complications may arise in administering the treatment.	"We'd like to think that we would never give something with the endotracheal tube not being in good position, but that could happen." (Neonatologist – 16)	2
	I have some safety concerns using other babies stem cells.	"You're giving a biologic product as opposed to a pharmaceutical product. … it's going to be important that the source of this product be checked at least to the level that we would use for donor human milk." (Neonatologist – 16)	2
Intention	I intend on screening patients for the trial.	"As long as this research goes through the normal process of any research going on in Canada, going to the presentation of the project, going to the ethics board approval, going to the inclusion and exclusion and criteria, going to the material resources, we are more than happy to be part of it." (Neonatologist – 15)	12
	My intention to screen would depend on baby's stability and gestational age.	"As a clinician I would want to see some degree of stability, so a baby who is in an acute deterioration, I don't think it would be the right time to either approach them or consider a research intervention." (Neonatologist – 9)	7
Goals	Screening for this trial competes with other priorities.	"Our clinical service is extremely busy when we're on-service … and we would not have time for any activities that are not directly related to patient care. So research often sort of falls by the wayside." (Neonatologist – 10)	7
	It is a high priority to reduce BPD.	"Everything what can reduce BPD, it would be great. Whatever research it is which helps to reduce the percentage of babies who get BPD, it has a high priority." (Neonatologist – 3)	6
	It is important to support research.	"I'm very keen in participating in research studies, especially studies like this that I think are very, very important and are going to pave the way to new therapy to improve the outcomes in our patient population, which is by the way getting worse because we're not doing better at BPD populations" (Neonatologist – 13)	4
Social, professional role and identity	Identifying or screening is not part of my role.	"In our setting, we have a research team. … That's their job, so they don't have a higher priority. They would always be able to identify them. That's their job." (Neonatologist –3)	11
	My role is to identify patients for the trial.	"I think we all at tertiary care centers should be involved in research and we should be supporting research. So yes, I think it's part of our job description." (Neonatologist – 4)	4
	Neonatologists should be involved in providing medical information and answering family's medical questions.	"Where you want the help from a neonatologist is maybe to approach families to explain the study, to explain the risk benefit because that might not be an easy study to sell." (Neonatologist – 2)	4

A strength of our study was that both parents and neonatologists participated, providing us with the perspective of both key groups in the planning of an early phase clinical trial. We emphasized the recruitment of parents who had a recently born very preterm baby and believe their views more closely reflect those of prospective trial participants (as opposed to a retrospective account months later). However, the severity of their infant's respiratory illness was not taken into consideration for this study. Thus, we might have interviewed some parents of "too healthy" infants who would not have been considered for recruitment in the clinical trial. An additional strength was the use of the comprehensive TDF framework, which allowed us to identify not only barriers that would have likely surfaced in any interview approach, but also unanticipated barriers.

Our study also had some limitations. One limitation is that other groups, including research assistants, nurses, and respiratory therapists, could have provided valuable insight but were not interviewed; future research should consider including their perspectives. Also, although neonatologists were recruited from across the country, parents were only recruited at 1 center. This decision was deliberate to ensure that parents could be invited and interviewed in person in a timely manner at the time of delivery as opposed to retrospectively after discharge. Nevertheless, as shown in **Table II**, parents recruited reflect a diversity sample across sex, parent age, gestational age, ethnicity, income, and education. We acknowledge the generalizability of our findings for parents might be limited and future research could consider interviewing parents from multiple centers.

Our study focused on the parents and caregivers perspective to identify important barriers to participation in an early phase clinical MSC trial. These results will inform and enhance trial design for early phase clinical trials by addressing the participants' knowledge gaps, adapting to the parents' desired approach (whom, when and how) and focus on optimizing institutional support for research. ■

We acknowledge the participating parents and neonatologists for their valuable contribution. We also thank Chantal Horth, research coordinator, Children's Hospital of Eastern Ontario.

Submitted for publication Dec 9, 2018; last revision received Feb 22, 2019; accepted Mar 8, 2019.

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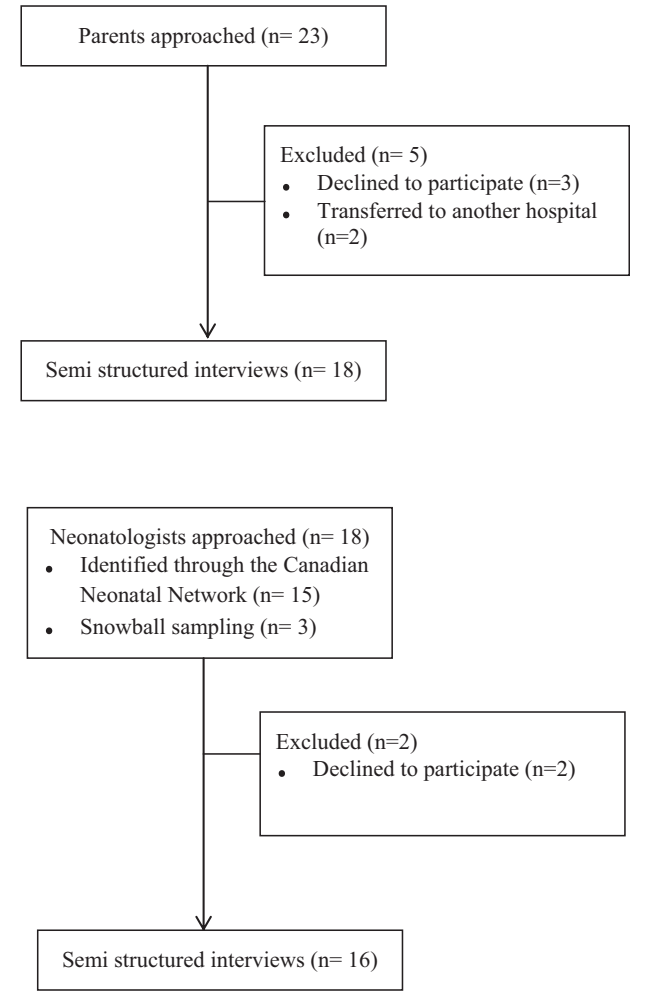

Figure. Flow diagram.