Barriers and Enablers to trial Optimization in the Neonatal Intensive Care Unit

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Abstract

For years, neonates have been "therapeutic orphans" and denied the benefits of clinical research because most therapeutic options are usually tested in the adult population. Most treatments and interventions have not been explored, and there is room potential rigorous, evidence-based clinical trials towards diseases specific to this population. Regenerative medicine holds great promise by potentially offering new ways of treating incurable diseases. However, bench to bedside translations often fail due to low recruitment rate. Thus, there is a need for effective interventions to increase trial participation and execution to help accelerate neonatal research. Behaviour theories could help to better understand trial participation, screening and recruiting behaviours, inform fit-for-purpose interventions, and assist in building cumulative evidence. There is a lack of clarity on the barriers and enablers to clinical trial participation from important stakeholder groups; NICU parents and research staff members. Study 1 reports findings on identified barriers and enablers that might affect parents' decision-making to participate in an early phase mesenchymal stromal cell (MSC) therapy trial including concerns with safety, efficacy and expected outcomes, but were willing to consider consenting to the trial after watching the animated video and having altruistic consideration. Study 2 reports findings on identified barriers and enablers that might affect research personnel recruitment to a multi-centre MSC trial which include: having cautious hope about the trial, importance of coordination with the clinical staff and study team and optimizing the study flow. Due to the challenging context of the study, the participants prefer to have clinicians involved with the recruitment. Lasty, Study 3 reports findings on identified barriers and enablers to screening potential patients for an adeno- associated viral vector gene therapy trial. Physicians were optimistic about the treatment but were concerned about the safety, feasibility, the expected outcomes of the treatment, and available resources (personnel, equipment, funding). Many expressed the need for support from clinical professionals prior to approaching parents and highlighted variability in screening roles. The resulting comprehensive set of factors helps to identify priorities for future research and provide insights towards developing novel interventions for neonatal research.

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Chapter 1: General Introduction

Every year, an estimated 15 million babies are born preterm[1]. Preterm birth complications are the leading cause of morbidity and mortality in infants worldwide[2]. Developmental immaturity affects a wide array of organ systems, increasing infant susceptibility to chronic diseases [3]. Pathological mechanisms of preterm delivery including inflammation and cytokine injury have severe implications for disease outcomes[3]. Most common ones are chronic lung disease, necrotizing enterocolitis, retinopathy of prematurity and brain white matter injury[3]. Due to rapid physiological changes occurring at early stage of development, and the limited knowledge of the pathophysiology of the specific diseases of infancy, finding effective treatment for these complications[4–6]. Research is needed to advance prenatal care to promote greater survival but also provide a better quality of life to neonates.

Clinical trials are essential for rigorously testing the safety and efficacy of new treatments in any population[7]. Yet, relative to other age groups, fewer trials are being conducted in the neonatal population[6]. There is a growing necessity to conduct all stages of trial development in neonates to uncover various diseases. Therapeutics used to treat neonates are derived from various safety profiles applied from older groups[6]. Neonates are still prescribed drugs in an off-label manner, whereby dosing regimens are derived from older adult/pediatric dose(s) and administered dose(s) is relative to the infant's bodyweight[6]. Among all trials registered within Clinicaltrials.gov dataset, out of the 22% (n=30,912) of pediatric trials, 0.2% (n=288) pertained to neonates[8]. The main therapeutic areas represented in the study were the cardiovascular system, the central nervous system, and anti-infective drugs; however, there is still limited research within this population[8]. Although there are lifesaving treatments in the Neonatal Intensive Care Unit (NICU), most treatments and interventions have not been explored, and there is room for potential rigorous, evidence-based clinical trials for diseases specific to this population.

Amongst new therapies deserving of clinical trials, regenerative medicine holds great promise by potentially offering new ways of treating incurable diseases; this avenue is new to both adult and neonatal populations. Rare diseases, including lethal and debilitating inherited disorders of surfactant metabolism can also impact the infants life and gene therapy, another novel and disruptive technology, may offer hope to substantially improve patient outcome. Maturation changes in the neonatal period present uncertainty of response to these new treatments. There is limited evidence for drug trials in the neonatal population and almost none on regenerative medicine therapies[3,9]. Clinical trials in neonates require careful design of study procedures, including recruitment strategy and safety assessment.

A desired area of focus to improve health outcomes in neonates is lung development[10,11]. There are many incurable lung diseases in neonates; current drug treatments in the adult/pediatric population cannot cure the lung diseases that are only seen in this population[5,11,12]. Tailored treatments should reflect the physiological characteristics of neonates; however, translating these innovative therapies come with some challenges. Given the complex, resource-intensive and intricate nature of these therapies, recruitment strategies must be optimized to promote timely evaluation and overall prevent clinical trial failure. Involving perspectives from important stakeholders, including neonatal parents and clinical staff, will help facilitate clinical trial

development. Thus, to disseminate new regenerative medicine treatments in the NICU would benefit from involving those who would be recruiting, delivering, and consenting to the trials.

Incurable Neonatal Lung Disease and Potential Promising Regenerative Medicine Therapies

Bronchopulmonary Dysplasia-the most common complication of extreme births

Bronchopulmonary dysplasia (BPD) is a chronic lung disease and a major complication of extreme preterm births (babies born 28 weeks or less, gestational age)[13]. BPD was first characterized by Dr. Northway in 1967 and was defined as a consequence of mechanical ventilation in the first week of life followed by long term supplemental oxygen treatment for respiratory distress[14]. However, this definition has changed over time, due to advancements in medical care and the administration of antenatal steroids, postnatal surfactant as well as gentle mechanical ventilation[15]. Currently, BPD is defined and characterized as the disruption of alveolar and vascular growth, causing larger and fewer alveoli, leading to decreased surface area for gas exchange[15]. BPD is considered a multifactorial disease that can potentially stunt lung growth due to factors such as inflammation, mechanical ventilation, and oxidative stress[14]. Unfortunately, long-term health repercussions of BPD are significant but not limited to respiratory and neurological impairments[16].

Despite modern clinical care, no effective treatment has yet been developed for promoting lung growth and repair since the discovery of BPD [16]. Treatments, such as postnatal steroids, decrease the overall incidence of BPD by reducing inflammation, however, have long term negative neurodevelopmental implications such as learning disabilities[11]. Other forms of treatment used in the clinic, such as surfactant, vitamin A and caffeine, can be used to cope with BPD, but not to reduce the incidence of BPD [11,17]. Thus, new therapies that both promote lung growth and repair are needed[18].

Mesenchymal Stromal Cell Therapy

Regenerative medicine, specifically stem cell therapy, offers promise to prevent/restore organ damage, including lung injury in extremely preterm infants. Stem cells are capable of self-renewal and have the potential to differentiate into a variety of cell types[5]. Among the different stem cell types, mesenchymal stromal cells (MSCs) are particularly useful in this context because of the cells' immunomodulatory properties[17]. In addition, MSCs exert pleiotropic effects through paracrine activity [17]. A systematic review and meta-analysis of preclinical studies evaluated the therapeutic potential of MSC in experimental models of BPD[19]. Alveolarization was the primary outcome of 21 studies involving hyperoxia-induced rodent models, and eight of those studies used umbilical cord derived MSCs, while 13 used bone marrow derived MSCs[19]. There is an interest of deriving MSCs from the umbilical cord because of ease of isolation and availability[17]. MSCs also have repair potential, included but not limited to: protect alveolar epithelial cells from oxygen toxicity, promote epithelial cell repair, decrease lung inflammation, and ultimately promote lung growth through the release of growth factors[5]. Furthermore, long term safety in lab models, showed persistent therapeutic effects; no sign of tumour formation and no enhanced risk of infections[19]. These promising pre-clinical studies provide a strong rationale to conduct a Phase 1 trial to test the safety and feasibility of cord derived MSCs in extreme preterm infants at high risk of developing BPD. Chang *et al*., reported the first Phase I clinical trial in South Korea with the administration

of these cells intratracheally[20]. Nine preterm infants between the gestational age of 23-29 weeks received a single dose of the treatment[20]. The researchers shown the treatment being feasible with no serious adverse events being reported[20,21]. They are now moving to a larger Phase II study focusing on infants between 23-24 gestation age, who are at the highest risk of developing BPD[21]. Efforts to understand the efficacy of the intravenous administration of these cells are ongoing and in the testing phase[5,18]. Recent publications show intravenous administration of the umbilical cord (uc) derived MSCs have consistent therapeutic effects in lab models[12]. Before advancing to the Phase 1 clinical trial, strategies are required to optimize translating this therapy from the bench to bedside in neonates. Concerns with novel trials include addressable barriers that impact one's decision-making relating to their participation in the trial[22]. It cannot be assumed that parents will necessarily consent to enrolling their extremely premature infant into the trial, without complete disclosure to address all concerns.

Inherited Diseases of Surfactant Metabolism

Genetic disorders disrupting normal surfactant metabolism have been identified as an underlying cause of respiratory disease in the pediatric population [23]. Pulmonary surfactant is a mixture of phospholipid and proteins that are synthesized and secreted by alveolar type II (AT2) cells[23]. Surfactant's protein B (SB-B) and C (SP-C) contribute to the surface tension-lowering properties[23]. Adenosine triphosphate-binding cassette member A3 (ABCA3) transports phospholipids into lamellar bodies, where the surfactant is assembled and processed [23]. Surfactant phospholipid and protein expression is regulated developmentally, increasing with advancing gestational age [23]. Mutation of (SP-B) associated gene (SFTPB) can result in abnormalities of surfactant production at birth, leading to lethal respiratory distress syndrome in neonates [23]. Surfactant metabolism disorder, a rare genetic disease, contributes to 25% of all severe lung diseases in neonates[23,24]. Current medical therapies, including corticosteroids and mechanical ventilation, can support pulmonary function, but many diagnosed infants need lung transplantation within 3 to 6 months of birth [23,24]. Lung transplantation is a rare medical procedure in neonates due to complication of size matching as well as preferential allocation of donor lungs for adults/older pediatric patients[23,25]. Moreover, mortality and long-term morbidities remain considerable for infants who undergo lung transplantation for this disorder, the most common being bronchiolitis obliterans[23,25]. A study looking at the long-term outcomes of lung transplantation of infants less than one year of age for this genetic disorder between 1993 and 2015 (n=28) showed that the overall 5-year survival rates of infants was 56%; seven infants were listed but died while awaiting transplantation[23]. Although lung transplantation offers interim therapy, new therapies that target gene replacement may help with survival.

Gene Therapy- Using Adeno-Associated Virus (AAV)

Modern genomics offers prospects for both discovery science and human health. It is set to change the face of modern medicine by increasing our understanding of genetic diseases and identifying novel disease targets for therapy. A genome engineering tool, recombinant adeno-associated virus (AAV) mediated gene, offers a new cutting-edge genome engineering technology for surfactant metabolism disorder [26]. AAV was first identified in the 1960s as an adenovirus isolate [26]. The viral genome consists of single stranded DNA molecule and is the most prevalent human isolate[26]. Targeted gene therapy for lung diseases is considered a promising treatment as intratracheal administration of the AAV vector can directly reach the cell type of interest. Pre-clinical data showed AAV gene transduction of associated surfactant gene (SFTPB cDNA),

restores SP-B expression, maintains lamellar body structure, and improve lung function in a unique mouse model of SP-B deficiency [24]. This vector also transduces human lung tissue, demonstrating its potential for clinical translation against this lethal disease [24]. Due to the lack of therapeutic options and unprecedented survival data, there is a rationale for clinical translation of the AAV vector [24]. The success of resource intensive novel trials depends on clinicians' willingness and capacity to participate and execute such trials. Much work needs to be done to identify clinician-related barriers to their trial participation.

Importance of Stakeholders Views to Optimize Clinical Trials

Although the MSC and AAV therapies seem to be on the verge of a potential breakthrough, the challenge is to demonstrate safety and efficacy before translating them into the clinic. Clinical translational of life saving therapies is slow and often fails[27]. Thus, for the Phase 1 MSC trial, multiple steps were taken before designing and seeking Health Canada approval (HULC-1, ClinicalTrials.gov NCT04255147). The Innovative Neonatal Cellular Therapies for BPD: Accelerating Translation of Research (INCUBATOR) was created to guide designing a feasible clinical trial. Part of the INCUBATOR platform involves drawing from knowledge translation methods to inform clinical trial design, and specifically to inform an understanding of barriers and enablers related to the involvement of various key stakeholders. For instance, a study conducted by Guillot *et al*., in 2018, interviewed parents of extreme premature neonates (between 22 to 28 weeks of gestation) and neonatologists to identify barriers and enablers of participating in a potential MSC trial[22]. In addition to the consent form, key barriers for parents include their lack of knowledge about clinical trial processes, concerns about the risks and side effects, and the need for comprehensive information relating to stem cells [22]. Importantly, parents reported preferring to be approached for recruitment directly by a neonatologist either before delivery or 1- or 2-weeks following birth[22]. After interviewing neonatologists about their barriers and enablers to trial participation, the following barriers were reported: recruitment of parents for participation in the study, competing priorities, time commitment, costs, and lack of institutional support[22]. Some identified barriers were unanticipated and could have compromised recruitment had they not been identified by this study.

Addressing the barriers for behaviour change (trial participation), mentioned from this study helped influence the design for the observational cohort in the upcoming Phase 1 MSC trial to treat BPD. The observational cohort served as a "run-in" phase for the investigative team and provided a measure of feasibility related to trial conduct. The observational cohort consisted of twelve patients that met the same eligibility criteria as the interventional arm (babies who will receive the MSC investigational product). Findings from Guillot *et al*., suggested taking a different approach to conveying the trial information to parents [22]. As a result, the team has created an informational video to show parents during recruitment[22]. The team interviewed with neonatal parents to evaluate the efficacy of the video prior to the launch of the Phase 1 interventional arm. The aim was to identify any barriers and enablers to the targeted behavioural of interest, trial participation. The same interview approach was applied to other stakeholder groups (recruiters and physicians), which is imperative for trial development and execution. The team interviewed research personnel who actively recruit participants, to understand barriers and enablers to recruitment for a multi-phase MSC trial. Furthermore, an early phase clinical trial with a novel, rationally designed AAV is in the works. The team also interviewed physicians to identify barriers

and enablers to screen patients with SP-B. The breakdown of each stakeholder group with the target behaviour of interest is shown in Figure 1.

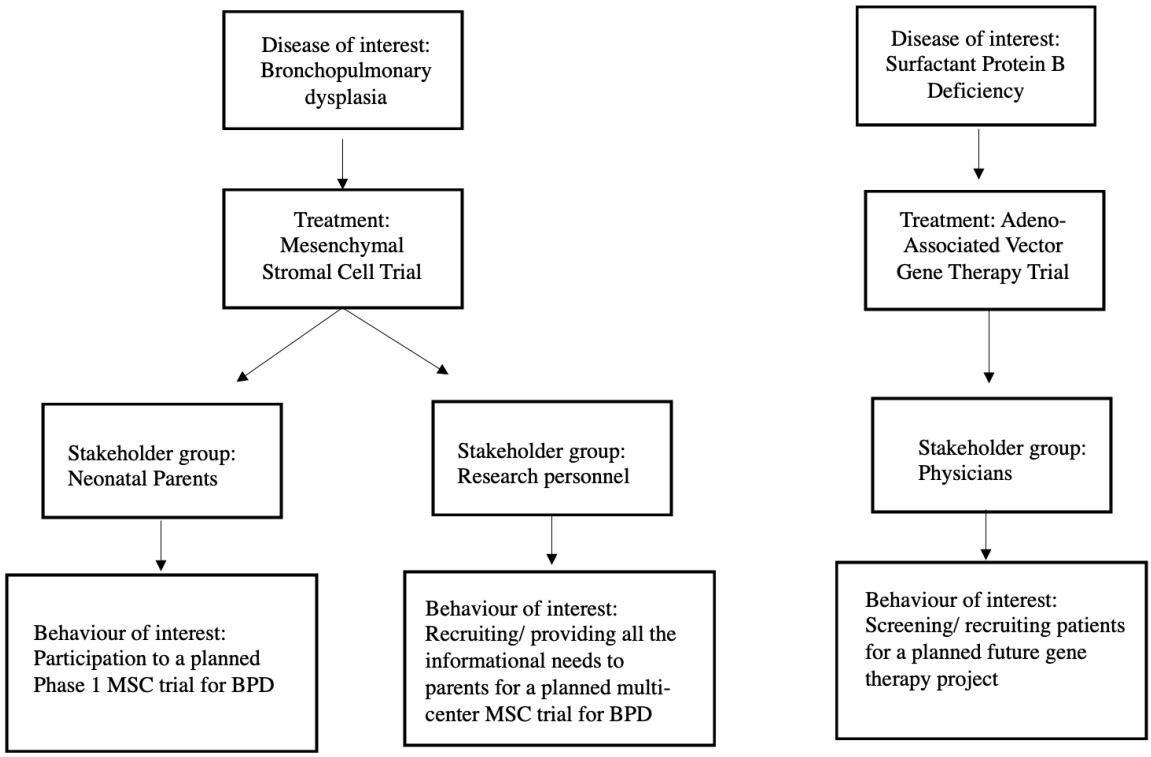

Figure 1. Behaviour of interest for all three stakeholder groups (Neonatal parents, NICU Research Personnel, and Physicians)

Parental Stakeholders- Providing all the informational needs to make an informed decision

Barriers to informed consent

Informed consent is the foundation of ethical practice of clinical research; it provides information to a potential study participant and enables them to make an informed decision about whether to partake in a research study [28]. Trials in neonatology are unique, as the consenter is a substitute decision maker (typically a parent), ruling on the behalf of their infant[29]. This can be challenging during the recruitment stage since the parent's decision-making process can be hindered by their heightened emotional state, including high levels of stress and anxiety[4,30]. For instance, Stenson and colleagues, reported that after 18 months, 12% of parents did not remember consenting to a study (n=34) [31]. This is concerning because parents who do not understand the study are prone to misinterpretation of the risks and benefits, which can lead to the regret of their participation[32]. [32]This instils an opportunity to improve the experience of parents during the consenting process to ensure best course of action can be taken.

The conventional consenting process typically involves a parent reading a consent form, followed by a face-to-face discussion with a clinical researcher/delegate, who is responsible for answering questions regarding the study[33,34]. The consenting process should provide all the essential information; however parents may feel overwhelmed by lengthy consent forms, resulting

in overseeing important information[35]. An Australian study interviewed parents (n=64) on their experience with the consenting process when enlisting their infants in a randomized asthma trial[35]. The study showed a small percentage of parents (12.9%) believed the trial was to provide a therapeutic benefit instead of testing safety and feasibility[35]. Moreover, only 19.4% of parents reported their belief that the signature page was to protect the infant's rights, while majority (40.3%) thought it was to protect the principal investigator's rights [35]. Alarmingly, less than half of the participants (45.2%) understood that they had the right to withdraw from the study at any time[35]. These results show a significant problem with the standard consenting process, and dynamic modes of delivery pertaining to trial participation are needed to better support parents in their decision-making process. For future neonatal trials, parents must be optimally supported when considering consenting their infant into clinical trials.

Barriers to participating in clinical trials

Predicting recruitment rate is important when planning, budgeting, and determining feasibility of a trial[36]. A 2015 analysis of registered trials reported that as much as 86% of trials do not meet recruitment numbers by the deadline, resulting in these trials experiencing delays or possible early termination (19%)[7]. Little is known about which factors influence conducting early regenerative medicine therapy trials for the neonatal population[22]. A systematic review reported a consent rate of 82.6% with respect to pediatric randomized controlled trials; however, one-quarter of trials had a consent rate of <70% [37]. Pediatric trials had a mean consent rate of 86.9%; this being slightly lower than that found in adult critical care studies, confirming added challenges[37]. Involvement of the parental stakeholder group voicing their thoughts and opinions on the trial design and participation can help overcome these challenges.

A qualitative interview study with parents of premature infants (n=34) investigated barriers to participate in research studies, with safety being one of the major concerns(n=10)[32]. The unknown risks of trials made many parents feel their infant was "being treated like a guinea pig"[32]. Few parents (n=4) decided to follow the standard of care procedures instead of participating in the trial, due to their anti-experimental beliefs[32]. Furthermore, Zupancic and colleagues conducted a similar study (n=101) and demonstrated that only a minority of parents (13%) would have not joined a study because of the complexity of the trial procedures [38].

Evidence shows other forms of communication help parents better understand research concepts compared to the traditional consent form[34,39–41]. Efforts to improve outcomes of informed consent include a wide range of modalities, including pamphlets and simplified documents listing key elements of the trial[42]. Although these documents have the potential to deliver key information including risk conveyance and formal consent materials, they may lack the information to address any concerns from parents about trial procedures and outcomes[42]. Presenting content heavy materials to parents can be overwhelming[34]. Alternatively, providing overly simplified information can create a situation where parents passively consent without understanding the implications of the study [34]. Presenting a well-designed study in an attractive manner and having repeated discussion with the parents about the progress of their baby may result in having a consent rate above 60%[3]. Incorporating a multimedia component in the research design can also improve participants understanding[43]. For example, a study involving adult participants (n=150) tested their understanding of their upcoming knee arthroscopy surgery [39]. The participants were randomized to a video (n=73) or a verbal consent group (n=77)[39]. Participants in the video group viewed a

multimedia element prepared by the American Academy of Orthopedic Surgeons[39]. Participants in the verbal consent group received information by an assistant [39]. Participants who watched the video had a 40% greater comprehension compared to those receiving a verbal consent[39]. Each group was presented similar information, but the video presented the information in a way that improved participant understanding[39]. Another study conducted semi-structured interviews with 24 mothers, who were being asked to enroll in a parenting intervention study[44]. The mothers received a summarized leaflet of the trial procedures, in addition to an educational video, and were followed up by an interview with the researchers[44]. The results from the study indicate that mothers generally had a positive outlook after viewing the video; having a key study member featured in the video brings a level of comfort. Furthermore, they suggest that a hybrid of paper-based and multimedia-based sources would enable participants to make a highly informed decision[44]. Having an alternative means of presenting trial information may be beneficial to achieve recruitment numbers. Involving parent partners early into the trial design allows the researchers to incorporate their views and address any unforeseeable barriers. Having participants review the recruitment material can improve the consenting tools to be used in future trials. Thus, close involvement of parents at all stages from trial design to execution is imperative.

Issues in standard processes of recruitment and consent for clinical trials can unnecessarily slow innovative research in the neonatal population. It delays promising therapies from reaching those in need. It is essential to work with parents to understand and address unanticipated impediments they may experience that the researchers are not aware of.

Clinical Staff Stakeholders- Importance of physicians' and research coordinators' perspectives of early phase NICU research

There has been little effort to gather information pertaining to the school of thought belonging to neonatologists and research personnel (including assistants and coordinators) in early phases of clinical trial development in the neonatal population. The NICU has a unique culture where preterm babies are extremely vulnerable to mortality and morbidity, thus investigators interested in exploring therapeutics in neonatology, should engage with other research staff prior to development of research procedures [3]. Recruiting parents for a Phase 3 trial compared to a Phase 1 trial differs substantially when safety and feasibility is better established, and the trial outcome focuses on measuring benefits[45]. Clinical researchers play a key role in the implementation of clinical trials. They contribute directly to the recruitment and execution of clinical trials[46]. Designing a robust clinical trial requires effective planning in conjunction with clinical staff input, including research personnel and physicians. A study revealed that clinical researchers perform more than 128 different responsibilities[47]. Clinical researchers are important to respond to study complexity by assuring study quality and protect study participants considering issues in research ethics by various actions such as screening and recruiting study participants, ensuring informed consent, collecting, and recording data and supporting follow-up. The involvement of clinical researchers is known to be associated with efficient, higher quality trials. The investigator is responsible for the overall conduct of the study, but the clinical researcher is responsible for the daily activities[47].

A range of factors can influence research clinicians' recruitment of patients into an interventional trial, which involves the testing of an investigational product. Clinicians voiced a

few barriers including: the fear that the introduction of research may place undue burden on parents, safety concerns of the investigational product, and the study being more resource intensive than anticipated[3748]. Several clinicians also acknowledge emotional and intellectual challenges while deciding to approach a potential participant as well as numerous communication difficulties when discussing early phase clinical trials with participants[37]. Understanding and identifying these factors early will ensure that they can be addressed before trial launch amidst promoting recruitment, retention, and successful trial completion. Each neonatal unit varies in their ability to take on clinical trials including but not limited to treatment preferences, shortage of resources, issues with consent and information[22]. Involving essential partners like clinical staff will help ensure the focus is on their priorities throughout trial implementation. No study can be executed by the study team alone, and by incorporating these key stakeholders, the study will not only build a clinical research network but also help develop an achievable study.

Trials in neonates is challenging given the study population. To develop novel interventions and increase recruitment rates, there is a need for a better understanding of modifiable factors and addressing them. A common issue with translating research from the bench to bedside is a lack of clarity in the description and definition of its components. Many observations can be drawn from knowledge translation science and be applied to these trials. Drawing from a list of possible barriers and enablers would help to find consistency across trials and stakeholder groups. A big advantage of drawing from knowledge translation frameworks is that they can link barriers to fit-for-purpose solutions and go beyond 'information and knowledge' as the main concerning factor[49]. Therefore, interventions to improve trial execution may benefit using theory informed qualitative approach for trial development. Using a comprehensive, evidence-based framework and prioritizing stakeholders' voices in advance of starting our clinical trials ensures discovery of prominent barriers and enablers. Addressing this wide array of hurdles in early phases of clinical trials (MSC and AAV gene therapy trials) can enhance the recruitment and trial execution for these studies and future studies.

Selecting Behavioural Theories

A challenging quality of selecting a theory to guide trial development is identifying constructs associated with the behaviour and theories incorporated within those constructs. Many theories have significant overlapping themes used in behavioural prediction and there is little guidance to choose the right theory to study. In response to the significant overlap of constructs in behaviour theories, a framework that synthesizes factors across theories can be helpful to make sure such a range of elements are considered. One such framework is the Theoretical Domain Framework (TDF), which can be used to understand the enablers and barriers to stakeholders' decision-making in the context of neonatal trials. This framework is known to impact behaviour, which can be used to inform qualitative interviews and provide a systematic approach to address barriers and enablers. These, in turn, influence decisions and actions, which can be used to help develop support for parents and clinicians that directly address these barriers and enablers[50,51]. The TDF is based on a synthesis of 33 theories and 128 constructs included in those theories are, 12 domains to maximize the accessibility and utility of behaviour theories[50]. The TDF was later validated and refined in 2012 to include two more domains, totalling 14, to explain behaviour[50]. In the second version, *beliefs about capabilities*, *beliefs about consequences*, and *motivation* &

goals were all split up into two new domains, while the nature of behaviour domain was removed. Both versions of the TDF are shown below in Table 1.

Table 1. Theoretical Domain Framework domains and associated definitions [50]

Domain (TDF-V1)	**Domain (TDF-V2)**	**Definition** [50]
Knowledge		Existing procedural knowledge, knowledge about guidelines, knowledge about evidence and how that influences what the participants do
Skill		Competence and ability about the procedural techniques required to perform the behaviour
Social/professional role and identity		Is the behaviour something the participant is supposed to do or someone else's? (When discussing 'we'/the collective) Boundaries between professional groups
Beliefs about capabilities	**Beliefs about capabilities**	Perceptions about competence and confidence in doing the behaviour
	Optimism	The confidence that things will happen for the best or desired goals will be attained
Beliefs about consequences	**Beliefs about consequences**	Perceptions about outcomes and advantages and disadvantages of performing the behaviour or pervious experiences that have influenced whether the behaviour is performed or not
	Reinforcement	Increasing the probability of a response by arranging a dependent relationship, or contingency, between the response and a given stimuli
Motivation & Goals	**Intention**	Conscious decision to perform a behaviour or a resolve to act in a certain way
	Goals	Priorities, importance, commitment to a certain course of actions or behaviours intentions
Memory, attention, and decision making		Attention control, decision-making, memory, i.e., is the target behaviour problematic because people simply forget?
Environment context and resources		How factors related to the setting in which the behaviour is performed (e.g., people, organisational, cultural, political, physical and financial factors) influence the behaviour
Social influences		External influence from other people, views of other professions, patients and families, doing what you are told and how that influences what you do
Emotion		How feelings, affect (positive or negative) may influence behaviour
Behaviour regulation		Anything aimed at managing or changing objectively observed measured actions
Nature of Behaviour		Relates to the history of the behaviour, and one's experience with said behaviour

Although initially designed to identify factors affecting health professional behaviour in the implementation of new innovations, the TDF has been since applied to patient related health behaviours as well [48,52]. Since its conception, it has been useful in identifying enablers and barriers to certain behaviours, such as participation in an early phase cancer trial in addition to recruitment and feasibility challenges for early phase adult clinical trials[4652]. Behaviour change interventions use different strategies and behaviour change techniques (BCT) to promote behaviour change[49]. BCT is defined as "an observable, replicable, and irreducible component of an intervention designed to alter or redirect causal processes that regulate behaviour; that is, a technique is proposed to be an 'active ingredient'" [49]. Applying these active ingredients (e.g., self-monitoring, goal setting, information about health consequences) to interventions focusing on stakeholders

behaviour of interest including trial participation can facilitate behaviour change [49]. Researchers used this technique and showed the feasibility and usefulness of applying the BCT taxonomy to characterize active ingredients for interventions managing diabetes[53]. The results from the study showed that the most identified BCTs were prompts/ cues, instruction on how to perform the behaviour, information about health consequences, social support, and goalsetting[53]. However, the novelty of this dissertation is drawing upon methods from both implementation science and knowledge translation science and applying the methods upstream to understanding and supporting trial stakeholders in early phase neonatal clinical trials.

Research in neonates has been neglected due to a series of challenges. It is clear there is an ethical requirement to give this population safe and effective treatments. The MSC and the AAV gene therapy trials will evaluate therapies that have the potential to provide a new outlook to improve care of incurable lung diseases. It is evident that there is a knowledge gap in the literature of the feasibility of conducting early phase regenerative medicine clinical trials with this delicate population. This thesis will focus on applying the TDF to identify key barriers and enablers of trial participation with parents, clinical research personnel and neonatologists prior to running clinical trials. It will also advance scientific knowledge and set a foundation of perceived barriers and enablers to early phase clinical trials in the NICU.

Rationale

Regenerative medicine intervention research may not have entirely engaged in behaviour change techniques, as few interventions have incorporated the use of behaviour science in their development of clinical trial designs. There is a lack of clarity on the barriers and enablers to clinical trial participation of NICU parents and medical staff members. To evaluate novel interventions, provide optimal support and education to parents of the trial, and provide successful trial recruitment for research personnel, there is a need for an in-depth understanding of the barriers and enablers associated with each stakeholders' role in the trial(s).

Thesis Outline and Objectives

The overall aim of this thesis addresses the aforementioned research gaps. The remainder of this thesis is organized in an article-based format and divided into 4 chapters:

<u>Thesis Hypothesis</u>

We hypothesize that by using the TDF to investigate and address barriers and enablers that influence clinical trial participation with the key stakeholders, will ensure optimization of trial development, recruitment, and ultimately trial completion.

Chapter 2: In this chapter we developed and evaluated a video to support parental needs in deciding to consent a Phase 1 MSC trial

> **Objective:** Assess whether an animated video explaining a Phase 1 MSC trial conduct addresses parents' informational needs identified after reading a standard consent form required to make an informed decision

Chapter 3: In this chapter we explored research personnel's barriers and enablers to consenting and addressing informational needs during trial recruitment

> **Objective:** Identify barriers/enablers to clinical research coordinators across Canada recruiting to inform early phase clinical MSC trials and future trials

Chapter 4: In this chapter we explored clinicians' barriers/enablers to screening and recruiting for a gene therapy trial

> **Objective:** Identify barriers/enablers to Canadian and German clinicians recruiting to a novel clinical gene therapy trial using an AAV vector for SP-B deficient neonates

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Chapter 2: Parents' views on an educational video to support their decision making in trial participation

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Abstract

Background: Bench-to-bedside translation is extremely slow and only a small portion of high impact preclinical therapies are successfully translated into practice. Unfortunately, many trials fail due to a low recruitment rate, ultimately slowing novel practical therapies and their clinical application. Improving the consent process is vital to successfully reach recruitment goals. Incorporating multimedia tools can enhance the consenting process and participants' enrollment. Prior to launching a Phase 1 Mesenchymal Stromal Cell treatment for Bronchopulmonary Dysplasia (BPD) in extreme preterm babies, we aimed to develop an informational animated video and identify any barriers and enablers to trial participation.

Methods: We developed an animated video to address previously identified decision-making challenges to aid parents considering enrolling their extreme preterm child into a Phase 1 MSC trial for BPD. We used the Theoretical Domains Framework (TDF) as a basis for conducting one-on-one semi structured interviews with parents of preterm infants. Parents with extreme preterm infants admitted at the Ottawa Hospital Neonatal Intensive Care Unit (NICU) were recruited. Ten parents were recruited with infants that were <28 weeks of gestational age (GA) and mechanically ventilated (on oxygen support) and four parents were recruited, with infants that were <30 weeks GA and not mechanically ventilated (not on oxygen support). The interview session consisted of parents reading the standard Phase 1 consent form, followed by a series of questions developed using the TDF. They were shown the animated informational video designed to address previously identified barriers using behavioral change techniques (BCTs). Upon completion, parents were asked similar questions to assess whether the video sufficiently addressed their informational needs. We used the TDF and directed content analysis towards identifying relevant domains based on frequency, relevance, and the presence of conflicting beliefs.

Results: We interviewed 14 parents. Key barriers parents expressed included wishing to know more about the safety, efficacy and expected outcomes after neonates receive the treatment (TDF domains: knowledge, beliefs about consequences). Parents were motivated to consent their child by altruistic consideration, regardless of the endpoints for an early phase trial (domain: goal and intention). Most parents expressed the importance of the presence of a physician available to discuss the trial with them prior to their decision-making; having the main investigator in the video present was negligent (domain: social influence). Majority voiced that having the video is a useful informational tool to help their decision-making over having the Phase 1 consent form and more inclined to participate in the trial (domain: environmental context and resources and intention).

Conclusion: The animated video incorporated elements of implementation science, knowledge translation science, application of the TDF and BCT. We were able to identify barriers and enablers that might affect parents' decision-making to participate in a MSC trial. The goal of this study is to optimize trial recruitment by integrating parents' perspectives and address these factors prior to using the video in the Phase 1 MSC trial.

Introduction

Significant progress has been made in the past few decades in stem cell therapy research for various diseases[1]. Mesenchymal stromal cell (MSC) offers a promising new treatment option for neonatal diseases, including Bronchopulmonary Dysplasia (BPD)[2]. BPD is defined as the need for supplemental oxygen at 36 weeks postmenstrual age (PMA) and is the most common cause of pulmonary morbidity in premature infants[2,3]. Approximately 40% of infants born between 22 to 28 weeks of gestation are diagnosed with BPD[4,5]. Since the discovery of BPD in 1967 by Northway *et al*., there has been no solution to promote lung growth and repair, and those who are affected have lifelong health consequences[6]. Pre-clinical evidence suggest that MSCs can help repair and restore organ damage (i.e., premature lungs) and may be a solution for improving the respiratory outcome of premature infants[7].

Trials in neonatology are unique as the consenter is not the patient, but rather a substitute decision maker (typically a parent), consenting on the behalf of their infant[8]. A challenging component to pediatric clinical trials is low recruitment rates[9]. This is a concern for Phase 1 trials, where there is no direct therapeutic benefit, and the trials carry significant adverse events[10]. Obtaining parental consent relies on providing the necessary information to parents, however, failure to provide important information may lead to difficulties in the decision-making process[11,12]. Consent rates in neonatal research ranges from 48-71%, however studies have shown the use of the conventional consent form is not an ideal source of information for participants[12–14]. Reasons for parents declining consent include but are not limited to emotional distress, uncertain risks, confusion with study procedures and lack of understanding of medical terminology[12–16]. Growing evidence suggests that using multi-media platforms may provide greater clinical trial comprehension compared to traditional paper consent forms; they facilitate the process of decision-making by increasing comprehension, satisfaction, and decreasing overall anxiety[17,18]. A study comparing a conventional informed consent document and a video on basic research concepts showed that 67.9% of parents preferred to receive trial information from the video[15].

Given the complexity and resource intensive experimental treatment of MSCs, recruitment strategies must be precise. Results from a past research study conducted by Guillot *et al*., in 2018, interviewed parents of neonates between 22 to 28 weeks of gestation, to identify barriers and enablers of participating in a potential MSC trial[19]. Key barriers for parents include their lack of knowledge about clinical trial processes, concerns about the risks and side effects, and the need for comprehensive information relating to stem cells[19]. Importantly, parents reported preferring to be approached for recruitment directly by a neonatologist[19]. They did express an interest in learning about stem cell therapy, the potential benefits, and study outcomes[19]. The participants encouraged researchers to explore different communication modalities to deliver the trial information. Key enablers for trial participation include altruistic health benefit and having positive views towards the research process. Majority agreed to enroll their child into the trial, even after understanding the potential complications[19]. These findings also align with another study looking to use these cells for stroke patients[20]. Results showed participants of the trial being optimistic about the potential benefits to participating in a MSC treatment, regardless of the uncertain risks[20]. The participants also noted having resources and information about the intended cell product would aid in their decision-making[20]. Work has been done exploring how to optimize recruitment strategies, however, there is no universal fit-for-all recruitment plan[19–21]. Since a Phase 1 MSC trial is resource

intensive, integrating views of parents early on into the development of the trial can help with trial execution.

Behavioural theories provide a framework for identifying modifiable factors associated with behaviour[22,23]. The Theoretical Domain Framework (TDF) is unique in that it draws on decades of behavior change research and synthesizes the constructs from 33 behavior change theories spanning 12 broad domains that were later validated and expanded into 14 domains, shown in Table 1[22,24,25]. The domains include factors known to affect decisions and actions that help understand the different barriers and enablers that might influence the target behaviour[26]. This is a useful framework to develop strategies consistent with behaviour change theory to address barriers and enablers of a given behaviour [22,24,25].

The Behaviour Change Technique (BCT) is a great tool used to link identified barriers to solutions. A comprehensive BCT taxonomy has been developed through an international consensus, resulting in Behaviour Change Techniques Taxonomy version 1 (BCTTv1), including 93 BCTs grouped within 16 categories with detailed definitions [25]. The BCT can be used to help characterize these active ingredients (e.g. feedback, self-monitoring, and reinforcement) in trials[27]. However, to our knowledge, no previous studies have used the BCT in the context of addressing barriers to trial participation identified by the TDF.

Here, we aim to address known barriers and enablers identified by Guillot *et al*., [19] and by using the TDF in conjunction with the BCT taxonomy, we were able to develop an informational animated video to be used during consenting for the Phase 1 MSC trial. We aimed to evaluate the video by using qualitative interviews informed by the TDF. The purpose of this research is to evaluate if the educational video supports participants ability to make an informed decision to trial participation in comparison to the Phase 1 consent form.

Table 1. Theoretical Domain Framework domains and associated definitions

Domain (TDF-V1)	Domain (TDF-V2)	Definition [31]
Knowledge		Existing procedural knowledge, knowledge about guidelines, knowledge about evidence and how that influences what the participants do
Skill		Competence and ability about the procedural techniques required to perform the behaviour
Social/professional role and identity		Is the behaviour something the participant is supposed to do or someone else's? (When discussing 'we'/the collective) Boundaries between professional groups
Beliefs about capabilities	**Beliefs about capabilities**	Perceptions about competence and confidence in doing the behaviour
	Optimism	The confidence that things will happen for the best or desired goals will be attained
Beliefs about consequences	**Beliefs about consequences**	Perceptions about outcomes and advantages and disadvantages of performing the behaviour or pervious experiences that have influenced whether the behaviour is performed or not
	Reinforcement	Increasing the probability of a response by arranging a dependent relationship, or contingency, between the response and a given stimuli
Motivation & Goals	**Intention**	Conscious decision to perform a behaviour or a resolve to act in a certain way
	Goals	Priorities, importance, commitment to a certain course of actions or behaviours intentions
Memory, attention, and decision making		Attention control, decision-making, memory, i.e. is the target behaviour problematic because people simply forget?
Environment context and resources		How factors related to the setting in which the behaviour is performed (e.g. people, organisational, cultural, political, physical and financial factors) influence the behaviour
Social influences		External influence from other people, views of other professions, patients and families, doing what you are told and how that influences what you do
Emotion		How feelings, affect (positive or negative) may influence behaviour
Behaviour regulation		Anything aimed at managing or changing objectively observed measured actions
Nature of Behaviour		Relates to the history of the behaviour, and one's experience with said behaviour

Methods

In preparation for HULC-1 (Helping Underdeveloped Lungs with Cells) a Phase 1 MSC trial (ClinicalTrials.gov NCT04255147), we conducted an observational study to test safety and feasibility of the trial conduct. The consolidated criteria for reporting qualitative research (COREQ) reporting guideline was used for this study[28]. The checklist guided the research methods, findings, analysis and interpretations[28]. Within this observational study the video was tested and evaluated for providing all the informational needs to parents, prior to being used as a consenting tool for the Phase 1 trial. The study was approved by the Ottawa Health Science Network Research Ethics Board and CHEO (20190628-01H). Verbal informed consent was obtained from all participants, and all procedures followed were in accordance with institutional guidelines. This

study acted as a "run-in" to test the various study procedures including evaluating the animated video.

Video Development

The video was developed using the results from a MSC parental interview study conducted by Guillot and colleagues[19]. The barriers and enablers expressed by parents were addressed in the video. Out of the 14 possible TDF domains, 6 key domains were identified which influenced parental decision-making shown in Table 2. The video was developed based on these parental responses and the 5 key and barriers and enablers identified (*knowledge, environmental context and resources, behavioral regulation, beliefs about consequences, and social influence*). We incorporated evidence based BCTs to specifically address the barriers (Table 2). Throughout the script of the video, we mapped out the relevant six domains mentioned, and the corresponding BCTs using the recently developed Behaviour Change Techniques Taxonomy version 1 (BCTTv1) which was revised by a health psychologist (JP) (See Appendix A for the script).

The script was developed in collaboration with research partners, the Parental Advisory Committee (PFAC) at CHEO, and two families in the NICU who have given birth to babies less than 28 weeks gestational age We used Guidance for Reporting Involvement of Patients and Public GRIPP2- short form, reporting checklist to report the research partners involvement with the revision of the script (Appendix B)Once the script was finalized, we reached out to Osmosis.org (professional didactic video production company) to produce the animated video, having a doctor as the lead character. The video incorporated the following, (1) voluntariness and the ability to leave the study at any time, (2) the cause of BPD and the potential MSCs have as a possible cure, (3) a case study of a baby (Olivia) with BPD, (4) the potential risks and benefits of the MSC, (5) role of regulatory bodies, and (6) discussed the regular standard of care. The information was presented in English (see Appendix C for screenshots of the video and the YouTube link for the video).

Table 2. Summary of relevant behaviours and enablers from interviews with parents and actions taken to address the barriers[19,23]

TDF domain	Specific belief (n=18)	Behavioural Change Techniques	Actions taken to address barriers with the video
Knowledge	"I do not know much about clinical trials and stem cells. I want to learn more about stem cell, potential benefits, risk and outcomes" (n=15)	Described procedural knowledge and incorporated a real-life example of a patient with BPD	Written into the script we defined BPD, stem cells and involvement of ethics committee, etc.
Beliefs about consequences	"I have concerns about the potential risks associated with MSC treatment" (n=17)	Information about health consequences→ emphasizing potential of stem cell research Credible source→ information presented by a reputable source	Provided information about health consequences including risks and precautionary measures taken. We decided to have the information presented by the Principal Investigator of the trial
Social Influence	The doctor is the key influential person (n-12)	Social support→ video is narrated by main investigator	Due to lack of time commitment of physicians we decided to have the video narrated by Dr. Thébaud for social support
Environmental context and resources	"It is important to have access to comprehensive information" (n=18)	Adding object to environment- animated video in lay terms played on iPad Social support (practical)→ provide practical help for informed decision making	The video's dialect is in in lay language and the video will be easily accessible via YouTube link
Behavioural regulation	"I suggest using different communication strategies to understand the clinical trial" (n=14)	Problem solving→video to keep parents engaged and help them understand the clinical trial Reduce negative emotions→ video to help with stress	Developed an animated video to help participants' decision-making

The interview guide development

We used the validated version of the TDF and kept the domain that was removed from the validated version (nature of the behavior) because it captures unique information helpful in understanding participant experiences with participation in a clinical trial [24]. The 15 domains used in this study are presented in Table 1. We developed a semi-structured interview guide from existing published interview questions that target attitudes, barriers, and facilitators to trial participation. The guide was developed in collaboration with a health psychologist (JP), NICU physician (BT), as well as NICU research coordinator (CH). We designed questions to explore barriers and enablers to trial participation after reading the Informed Consent Form and after

watching the animated video. The behaviour of interest is parental participation to a planned Phase 1 MSC trial for BPD, defined by using the Action, Actor, Context, Target, Time (AACTT) framework to ensure study of the specific behaviour shown in Table 3[28]. To ensure our questions were relevant and the phrasing was clear, we piloted our interview with one of our collaborating parent partners (see Appendix D for the interview guide).

Table 3. Action, Actor, Context, Target, Time[28]

Action	Participation in a planned Phase 1 MSC trial for BPD
Actor	Parents
Context	Neonatal Intensive Care Unit
Target	Parents of extreme preterm infants born <28 weeks gestational age at risk of developing severe BPD
Time	After 7 days of life ventilated

Sampling strategy

This observational study was offered to patients that fit the inclusion criteria (neonates born less than 28 weeks gestational age and ventilated for 7 days) and would have been eligible for the upcoming Phase 1 trial and fit the profile of a baby diagnosed with BPD (Arm 1). However, due to the impact of the COVID-19 pandemic and the low recruitment rate, we also included a subset of parents (Arm 2) whose neonates most likely do not fit the profile of a baby with BPD but can still provide valuable insight. This group of parents (study ID A#) only participated in the interview portion of the study; no other study procedures were conducted on their infant (see Figure 1 for the schematic of trial).

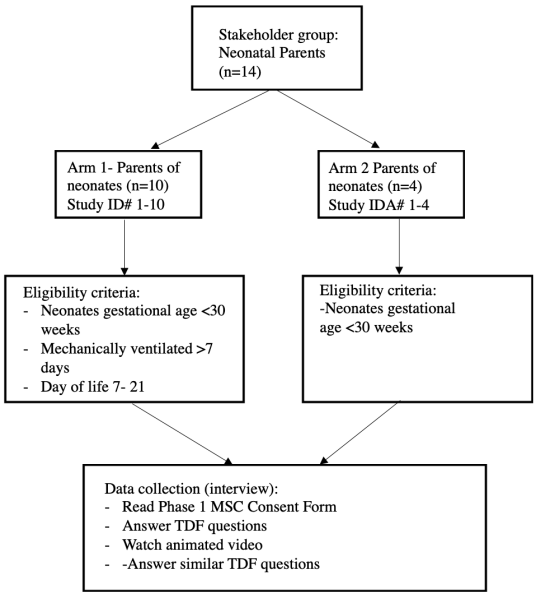

Figure 1: Schematic research design of the two individual study arms

A master's student (KS) with background in health science was trained in conducting interviews and using the TDF to inform data collection and analysis. KS conducted all interviews

via Zoom. Sample size was determined using a 10+3 stopping rule[29]. Saturation is an indicator of quality and trustworthiness in qualitative research. Thus, data was considered adequate (thematic saturation) if no new themes emerged within the last three consecutive interviews[30].

During the interviews, participants were encouraged to imagine they were eligible for the upcoming Phase 1 MSC trial to treat BPD. Parents responded to hypothetical questions regarding potential barriers and enablers to their trial participation. During the interview, we first asked the parents to read the Phase 1 consent form (see Appendix E), which was followed by asking catered questions regarding the document. After, we had the parents watch the 6-minute animated video and answer similar questions. KS explained the main goal is to understand if we have provided all the informational needs to support them to make an informed decision on whether to participate in the trial or not. All interviews were recorded, transcribed, and anonymized.

Data analysis

Using NVivo 12 (qualitative software), a directed content analysis was conducted[31]. The interviews were transcribed and verified by interviewer (KS) prior to analysis. The analysis involved the following steps consistent with standard recommendations for TDF-based qualitative studies:[22,24,26] (1) coding, which represents linking participants' responses to theoretical domain using a codebook, (2) generation of specific belief statements, which involves grouping a set of responses reported by different participants with similar underlying ideas and/or beliefs, and (3) identification of key theoretical domains [32]. Overarching key themes spanning the relevant domains were then generated.

Code book development and coding to TDF domains

The first two interviews were independently double-coded, and the two coders compared their coding to develop a coding book. The code book was developed to maintain coding rule transparency and help code the rest of the remaining interviews. Analysis was led by a primary analyst (KS) who coded each interview and allocating relevant experts into one of the theoretical domains from the validated TDF version[23,24,26]. A secondary analyst (GC), blinded to the primary researcher's coding, subsequently coded the excerpts to the TDF domains. Conflicts were resolved through discussion. The next two interviews were coded using the established code book. Assessment of inter-rate agreement using Kohen's Kappa was conducted for the second two interviews; a priori we planned that if kappa inter-rater agreement scores did not reach threshold (0.80), single coding would not occur for the remainder of the interviews[33].

Coded data excerpts were converted into belief statements-a collection of responses with a similar underlying belief that suggest a problem and/ or influence of the beliefs on the target behaviour[26] by KS and revised by a health phycologist (JP). Belief statements were compared within and across domains to generate and distinguish between specific subtemes[34]. To document the progression from data excerpt to subtheme, we created belief statement tables showcasing subthemes, belief statements, exemplary quotes, frequency counts (number of participants endorsing a belief) (Appendix F). We identified key domains according to frequency of beliefs, presence of conflicting beliefs, and relevance of recruiting behaviour [26].

Results

Participants

Interviews were conducted between December 2020 to June 2021 and lasted between 19 and 54 minutes (median, 33 minutes). Sixteen parents were approached for Arm 1. We enrolled 12 parents, and 10 interviews were completed. One parent declined to participate in the interview and one interview was completed for a set of twins that were enrolled. We approached nine parents for Arm 2 and enrolled six parents but only completed 4 interviews as two parents did not follow-up for their interviews. In total, fourteen babies were enrolled into the study: ten in Arm 1 and four in Arm 2. Six parents participated in the interview as a couple and the other 8 parents participated in the interview alone. Participant's characteristics are described in Table 4.

Table 4. Sample characteristics for parents of enrolled neonates (n=14)

Characteristic	**Enrolled neonates n=14 (%)**
One parent participated in interview	8 (57)
Father	5 (36)
Mother	3 (21)
Both parents participated in interview	6 (43)
Gestational age	
23	1 (7)
24	5 (36)
25	1 (7)
26	2 (14)
27	1 (7)
28	2 (14)
29	1 (7)
Mechanically ventilated at time of approach	
Yes	10 (71)
No	4 (29)
Age of parents	**Total number of parents n=20 (%)**
<25	1 (5)
26-30	8 (40)
31-35	9 (45)
36-40	2 (10)
Race	
White	8 (40)
Black	6 (30)
Other	6 (30)
Education level	
Less than high school	1 (5)
Highschool	4 (20)
University/ college	15 (75)

Inter-rater reliability

Data from research personnel were analyzed together and consisted of 67 belief statements across 12 domains (Appendix F), The first four transcripts were double coded by two researchers; kappa inter-rater agreement score for the four interviews was 0.935, indicating agreement and that interviews could be reliably coded into respective domains[33]. The remaining transcripts were then single-coded (KS).

We identified nine relevant domains: Goals, Social Influence, Knowledge, Beliefs about Consequence, Beliefs about Capabilities, Reinforcement, Environmental Context and Resources, Intention, Memory, Attention and Decision-Making. A comprehensive list of relevant domains detailed belief statements and subthemes associated with each domain are provided is shown in Table 5. In depth analysis of the belief statements can be found in Appendix G.

Table 5. Summary of belief statements and sample quotes from participants assigned to domains identified as relevant

Relevant Domain	Subtheme	Sample belief statement	Sample quotes
Key theme 1: Parents navigating choice in the face of uncertainty			
Knowledge	Existing knowledge about stem cells	I am somewhat aware of stem cells (8)	"I know some information about stem cells from documentaries and you see the potential it has to correct organs, so I know that there is potential for it"-Participant 11
		I am unaware of stem cells (6)	"I was coming in with very little information. There is a bit of curiosity there."- Participant 10
	Knowledge about stem cells after reaching ICF and video	I would like to know more about toxicity, and expected outcomes (9)	"Like this trial is a Phase 1 trial, I would want to know the expected outcomes. Explain what would happen or you got the results they wanted or didn't get."- Participant 3
		I would like to know more about the efficacy of the cells (1)	"I'm not really sure I understand how you identify the efficacy of the cells?"- Participant 2
		I would like to know more about the preclinical data after reading ICF (7)	"The only thing I noticed was with the dosage count, 1,5, and 10 million. It would be nice to have background on these numbers. Like why these numbers? What's the difference between each dosage? It's quite a big difference."- Participant A03
Beliefs about consequences	Expected and unexpected outcomes	Expected outcomes of receiving the cells (8)	"Information on risk involved or like worst case scenario, nothing will happen. Best case scenario we might see slight improvements, or these are the markers that we are looking for during the trial kind of thing to put me at ease. So, outcomes from the study"- Participant 10
		Clarity of likelihood of being diagnosed with BPD after watching the video (4)	"The video could kind of scare some parents, right? Because they're like my baby's on ventilation. Is this going to happen to my baby? So, like maybe making it clear like you said that this is an extreme case because that was not clear in the video"- Participant 3
	Safety and side effects	I am concerned about the potential side effects (after reading ICF and watching video) (9)	"I don't want my child to be a guinea pig. Obviously, it would to be like to benefit babies in the future and stuff but am I willing to risk my child's life to see if there is a benefit."- Participant 5
		Uncertainty with Phase 1 trials (5)	"The other study that we are participating in, has 1000's of participants. This Phase 1 only had 9 and I don't want my child to be the first to receive the cells"- Participant 5

	Treatment benefits	The trial will benefit future children (8)	"Like anything that could potentially benefit children in the future, so their parents don't have to go through as much of other NICU equipment."- Participant 3
Goal	Motivator	Give a better quality of life for my child (5)	"You want to prevent any negative effects, so you would want to give your child any treatment out there, like whatever to help benefit them"- Participant 11
Key theme 2: Influence from experts			
Social Influence	Research staff	I would want trial information from a research staff (5)	"I think it's fine with one of the research assistants providing information but making the neonatologists available for any additional questions if necessary."-Participant 3
	Neonatologists and bedside nurses	I trust the attending neonatologist and would want their opinion (6)	"For me I would reach out to my baby's doctor. If they feel alright, I would be more inclined to participant"-Participant 4
		I trust the bedside and would want their opinion (6)	"Practically speaking, like day-to-day, we see our nurses 100% more often than doctors, so I'm like you might get a couple of check-ins per week with a doctor, but the nurses would probably be more important."-Participant 2
	Perception of the video	The video advocates to prompt more questions (5)	"I think from the video it prompts questions. I think it is a good opportunity for a discussion without it getting too complex."- Participant A03
Memory, attention and decision process making	Factors influencing decisions	I would need to have a conversation with health care professionals (8)	"I think I would be more inclined to consider it. Yeah, I'm still not 100%. We still need to sit down with the doctors and stuff like that, but like this is very good"- Participant 10
Key theme 3: Ambivalent intentions			
Reinforcement	Previous clinical trial experience	I have experience with clinical trials (8)	"The lactoferrin study in the NICU had no fatality. So that's why I consented to that trial. There were 2000 babies already in the study so there's proof that it works. That is why we consented"- Participant 5
Intention	Intent to participate	I intend on participating in the trial after reading the ICF (5)	"I think so, I probably would."- Participant 2
		I intend on participating in the trial after reading the ICF after watching the video (10)	"If I was presented with video alone, I'd be more likely to say yes. If I'm presented with the consent form alone, most likely I would say no" Participant 1
	Intent to not to participate	I do not intend to participate after reading the ICF (2)	"Unless the wording of the consent form changed because it is 100% accurate. Like their exaggerating a bit to be on the cautious side, I would not participate."- Participant 11
	Conditional intent	I would only participate if there were no other option (4)	"Maybe if it was a life of death situation maybe I'll reconsider"- Participant 5
		I would rather participate in an efficacy trial rather than a safety trial (3)	"If it's solely just to test the safety of this procedure, I would say no to the trial. I am not sure what would really happen to my child"- Participant A03
Key theme 4: Enabling resources			
Social Influence	Perception of the video	Having ethics in the video is great (8)	"Knowing that there's an Ethics Committee and the extensive vetting that goes through this, at least here in Canada before things get put into place. Knowing that really helps"- Participant 10
Environmental context and resources	Enabling resources	The video is a great source of information (8)	"I'm a visual person, so I found the visuals quite helpful and less intimidating, I think as well, I could tell that the information was not to say less complex, but it was definitely accessible. Even if English wasn't my first

			language, I still would be able to identify and understand everything" -Participant 10
	The consent is not an ideal source of information	The consent for is not an ideal source of information (3)	"The consent form is exaggerating a bit to be on the cautious side. I felt like video, it is a little bit different than the consent form. The consent form is more like a legal document and the video is more informational. "-Participant 1
Beliefs about capabilities	Confident	I feel confident in my ability to make an informed decision after watching the video (5)	"More confident than when we just read the paper. When we read just the paperwork, I think we're both kind of like pass."- Participant A05

[a] Numbers in brackets indicate how many participants endorsed a specific belief statement

Key theme 1: Parents navigating choice in the face of uncertainty (domain: Knowledge, Beliefs about Consequences and Goal)

Before video view

Participants indicated a range of knowledge when asked about their familiarity with stem cells. Some (n = 8) indicated having heard about stem cells through school and media outlets (news and documentaries), while others reported no prior knowledge (n=6). Nevertheless, most (n=8) requested to know more about the risks and the expected outcomes relative to standard of care treatments. Parents also wished to know more about the preclinical data (n=7) specific to the dosing of cells (domain: Knowledge and Beliefs about Consequences).

After video views

The need for more information arose after viewing the video, in particular health concerns relating to the case study (n=4). Parents wondered about the unexpected outcomes after viewing the video, including the possibility of the diagnosis of BPD in their child. In addition, they questioned whether all children supported on mechanical ventilation will later be diagnosed with BPD. Others were concerned about the stem cell treatment and its side effects (n=9) (domain: Beliefs about Consequences). Five parents specifically mentioned the risks associated with participating in a Phase 1 trial, as there is insufficient data related to the safety of these cells (domain: Beliefs about Consequences).

Eight parents mentioned they would participate in this trial to benefit future neonates; they do not want other parents to experience the hardship of having a child in the NICU (domain: Beliefs about Consequences). Another factor parents mentioned behind their participation was improving the quality of life for their infant (n=5). One parent expressed the feeling of regret of not participating in the trial conditional upon the possibility of their child developing BPD (domain: Goal).

> "You want to prevent any negative effects, so you would want to give your child any treatment out there, like whatever to help benefit them"- Participant #11

Key theme 2: Influence from experts (domain: Social Influence, Memory, Attention and Decision-Making)

Before video views
When asked who they would like to hear the study from, five participants mentioned that hearing the trial from the research staff is sufficient as they can provide important details of the study (n=5). However, they mentioned that having the Principal Investigator available to answer questions will aid in their decision-making (domain: Social Influence).

Parents identified that opinions of attending neonatologists and the nurses would impact their decision to participate in the trial (n=6) (domain: Social Influence). They wished to have a conversation with the clinical team that understand their child's best health interests (n=8) (domain: Memory, Attention, and Decision-Making Process). One parent mentioned speaking with their neonatologist will influence their participation.

> "I think I would be more inclined to consider it. Yeah, I'm still not 100%. We still need to like sit down with the doctors and stuff like that"-Participant 10

After video views
After watching the video, parents mentioned having the principal investigator (neonatologist) present in the video demonstrated that he was taking accountability for the trial, and the video facilitates conversation (n=5) (domain: Social Influence).

> "Definitely having him in the video you can see and hear the actual person doing the study."-Participant 4

> "I think from the video it prompts questions. I think it is a good opportunity for a discussion without it getting too complex."- Participant A03

Key theme 3: Ambivalent intentions (domain: Intention and Reinforcement)

Before video views
Eight participants discussed how past experiences with clinical trials influenced their participation. Few parents were aware of other NICU studies prior to being approached to consent for this study. Upon comparison, one parent mentioned the hesitancy of consenting due to the difference in the samples size for a Phase 1 trial (domain: Reinforcement).

> "The lactoferrin study in the NICU had no fatality. So that's why I consented to that trial. There were 2000 babies already in the study so there's proof that it works. That is why we consented"- Participant 5

Few participants, after reading the informed consent form (n=5), said they would participate in the trial. Two parents mentioned that they would not participate in the trial because of the wording of the document (domain: Intention).

After video views
Ten participants mentioned, after viewing the video, they felt more knowledgeable of the trial and would likely participate (domain: Intention).

> "If I was presented with video alone, I'd be more like very likely to say yes. If I'm presented with the consent form alone, I'm most likely I would say no"-Participant 1

Few parents (n=4) considered participation if no other treatment option were available. Three participants said that they would reconsider the trial if there was a direct benefit to their neonate (domain: Intention).

Key theme 4: Enabling resources (domain: Environmental Context and Resources, Social Influence, Beliefs about Capabilities)

After video views
Parents agreed having the video component was a great source of information (n=8) (domain: Environmental Context and Resources). It brought organizational and interpersonal support, through clarity of the role of regulatory bodies and relatability using the example of baby Olivia (domain: Social Influence).

> "Knowing that there's an Ethics Committee and the extensive vetting that goes through this, at least here in Canada before things get put into place. Knowing that really helps"-Participant 10

After viewing the video, parents reported having a better understanding of the study procedures and the potential risks involved. Some interviewees (n=3) indicated that the informed consent form document is not an ideal source of information, as it included overwhelming medical jargon (domain: Environmental Context and Resources).

> "I'm a visual person, so I found the visuals quite helpful and less intimidating, I think as well, I could tell that the information was not to say less complex, but it was definitely accessible. Even if English wasn't my first language, I still would be able to identify and understand everything" -Participant 10

Few parents expressed that the video made them feel more confident in their decision to participate in the trial compared to reading the consent form (n=5) (domain: Beliefs about Capabilities)

> "More confident than when we just read the paper. When we read just the paperwork, I think we're both kind of like pass."- Participant A05

Discussion

Neonatal regenerative research can be very technical and complex to understand, and for parents with their infants in the NICU, a strong understanding of trial procedures is essential. In this study, we built upon the work from Guillot *et al*., identified barriers and enablers to trail participation with parents who were narrated a hypothetical scenario to participate in an Phase1

umbilical cord derived-MSC trial to treat BPD[19]. The purpose of this study was to understand what support parents required to make an informed decision. We developed and piloted an educational video describing the Phase 1 MSC trial procedures. After conducting the interviews, parents wanted to know more about the cell therapy as well as the unexpected outcomes. They expressed concerns of the risks and the potential impact it may have on their child's health. Regardless, many stated they would be motivated to participate in the trial to benefit future children and improve neonatal care. Parents who were keen to participate preferred to engage in a conversation with trusted experts (neonatologists, bedside nurses). By providing an informational animated video, in general, parents were more inclined to participate compared to only being given the consent form. This is an important finding as historically, investigators found greater enthusiasm from parents prior to participating in the trial[19].

Having accessible knowledge about the MSC therapy presented in the animated video was an enabler to facilitate participation. Parents preferred the animated video as an informational tool compared to the conventional consent form. This tool helped bring clarity to study concepts (stem cell administration, role of regulatory bodies and purpose of Phase 1 trials), allowing parents the opportunity to engage in patient-researcher conversations, leading to increased parent comprehension levels[11,35]. There was a similar finding from other researchers that investigated the use of multi-media tools during consent[18]. O'Lonergan *et al*., parents who were randomized to a multimedia consent process (Pretend Study to Determine the Amount of Muscle, Tissue, and Fat in Bodies) showed greater understanding of a hypothetical procedure than parents who completed a traditional paper consent process[36]. Overall, we found similar results where the video appears to fill in knowledge gaps after reading the Phase 1 consent form. This may be related to audiovisual stimulatory cues, allowing for more active learning in comparison to the standard consent form[11,18]. Having this option provides parents the time, comfort, and control to reexplore the information provided[18,21]. These findings resonate with Tait *et al*., with multi-media platforms being a clear and an effective way of communicating trial information[15]. Many parents did say they were more willing to consider participating in the trial after viewing the video compared to those reading the consent form. *Kass et al*, pointed out that longer consent forms do not highlight the important details of study procedures[11].

The role of the clinical care team is vital to parent's decision-making. Although given all the essential information and including the principal investigator in the video, many parents voiced the importance of having a conversation with the healthcare providers. Parents were content with the information presented by the researcher, however having bedside nurses and neonatologists available to answer questions was preferred due to their expertise[37]. Thus, educating clinical staff is important to the success of the trial[38]. Showcasing the importance of the study to clinicians and bedside nurses through comprehensive and ongoing training, can aid with advocating participation for the trial[39,40]. Delivering the message through the principal investigator is important, as the study encounters less resistance, and the investigator can answer any technical questions48,. Also, recognizing and appreciating the clinical staff's contribution to the study can help with participation[38].

Parents were motivated to participate in the trial to benefit future children but also expressed concerns about the risks associated with the MSC treatment. A recent review about the communication of misconceptions during Phase 1 trials, the patients had a mistaken understanding

of the therapeutic benefits; roughly 85% of patients were expecting physical benefits from their participation in Phase 1 trials[10]. One of our goals was to indicate to parents the purpose of the Phase 1 MSC trial. Our results suggests that the video made it clear to parents that there will not be a direct benefit and that the purpose of the trial was to assess the most effective dose. However, there was still hesitancy in participation due to the unknown outcomes of the investigational treatment compared to standard of care in the NICU. This was consistent with another research article, where parents voiced their concerns between risks of experimental treatment and clinical treatment[14]. It will be important to provide information on MSC cell therapy safety and efficacy and compare the findings to the standard of care[41]. Parents reiterated that having these key pieces of information will be beneficial to their decision-making. Expected outcomes and efficacy of stem cell research can be extrapolated from systematic reviews and given to parents to review[2,42]. This will also facilitate more conversation between the participant and the researcher[11]. Parents can evaluate the pros and cons of participating in the trial and use the BCT comparative imaging technique to visualize future potential outcomes when considering their participation[43]. Parents who did not have a higher education and less social support, displayed greater health seeking behaviours and were more inclined to participate in the trial, which also resonates with *Harth et al*., findings[44]. This finding may be explained by the benefits received by participating in the trial of reciving a new treatment product to help their ill baby. Another explanation may be that populations with low educational background may have low perception of risk involved in research and therefore would be more inclined with research[46]. The video clarified study procedures, but researchers can apply the teach-back technique, which involves asking potential participants to "teach back" key concepts, ensuring the parents understand the research study[35].

Strengths and limitations

The aim of the present study was to identify anticipated challenges to help optimize a planned Phase 1 umbilical cord derived MSC trial. One limitation is that we captured hypothetical barriers and enablers to participating in a Phase 1 umbilical cord derived MSC trial to treat BPD. In the future, when the first phase is launched, there is an opportunity to document barriers and enablers from parents who have enrolled their child into the study. There can be an assessment of the experienced barriers and enablers, and whether the trial recruitment activities sufficiently addressed anticipated barriers and enablers identified here. Another limitation that may arise is when highly invested parents who are pro-research, may be influenced to enroll their child in the trial, regardless of the risks[47]. This placebo effect may be why many substitute decision-makers were overly optimistic with the trial and did not fully reflect the expectations of prospective trial participants. Another limitation is having a mixture of couples and single parents participating in the study. Some couples would voice their thoughts together and not individually, therefore creating bias. It would be interesting for future studies, to interview parents separately. Nonetheless, further exploration is required to understand experiences of parents who are eligible for the Phase 1 trial. The strength of this study lies in the use of the BCT to link specific barriers to active ingredients, and to use those active ingredients to produce and evaluate the animated video. In addition, the use of the TDF to identify factors that impact trial recruitment also strengthens the study. The TDF gave a comprehensive assessment of the potential barriers and enablers to trial participation for an early phase MSC trial. By linking the research findings to the therapy, it allowed us to generate evidence-based strategies that other trialists can incorporate.

Conclusion

There is a need to establish best practices when approaching parents to participate in neonatal research, particularly early phase trials. News that their newborn is seriously ill can be devastating and stressful for parents. There is a lack of clear strategies to convey trial procedures to parents, which is likely to contribute to the neglect of neonatal research. A significant methodological goal was to demonstrate the potential benefit of alternate consenting tools that can be used to help with decision-making. Using qualitative methods, guided by a comprehensive framework, enabled us to identify barriers and enablers before trial launch, giving us the opportunity to develop trial-specific strategies based on the identified barriers and enablers. This was the first attempt to explore the utility and capacity of BCTs addressing known barriers and enablers to parental trial participation. We showed that it was possible to use the taxonomy that focuses on behaviour change by creating a consenting tool to be used in the trial. This study suggests that prospective trialists of promising therapies for neonates should explore different channels to convey research information to potential participants, hoping to achieve their recruitment goals, while supporting informed decision-making.

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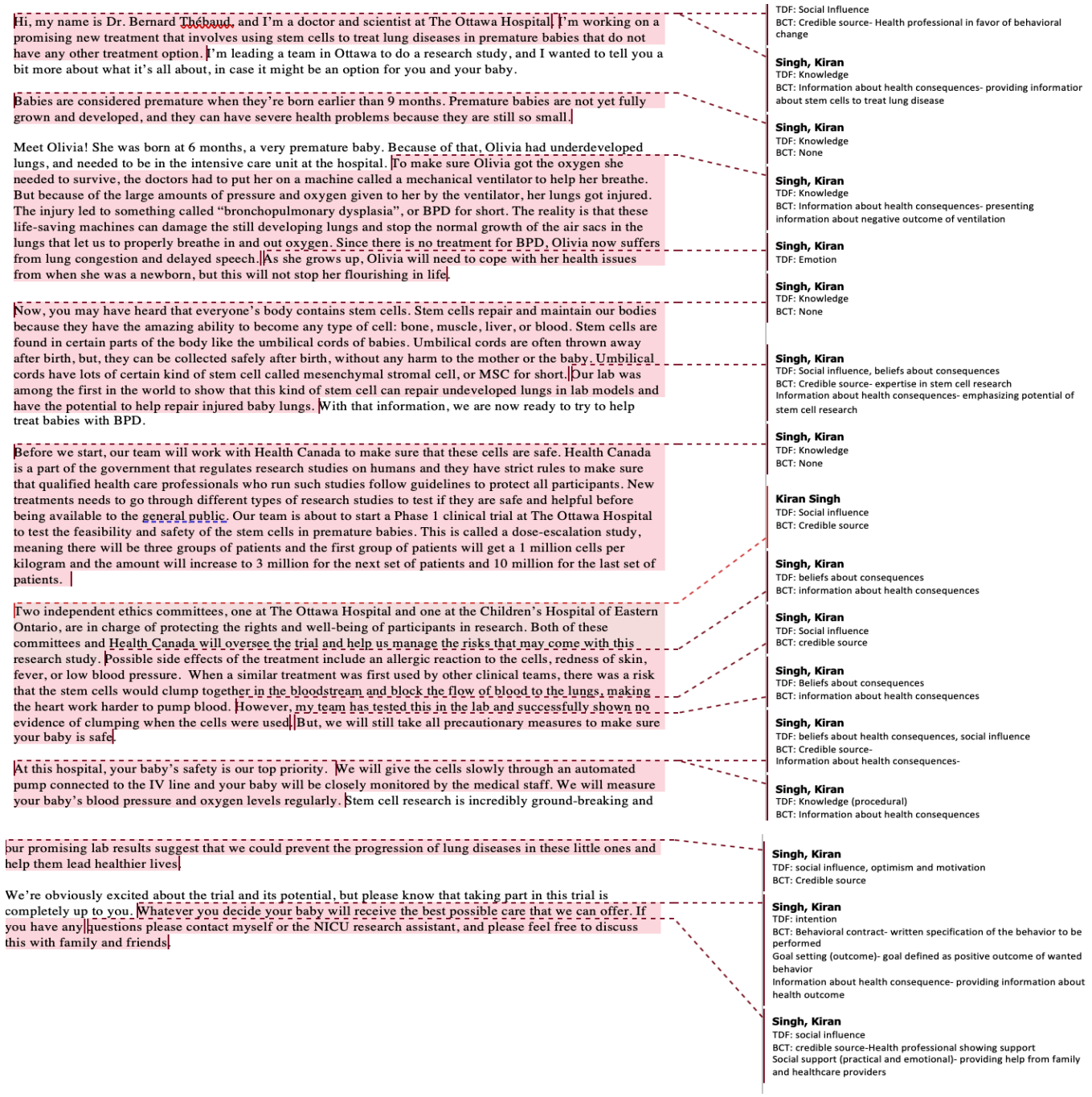
Appendix A- Animated Video Script



Appendix B- Animated Video Script

Check list item	Description
1. Aim Report the aim	To ensure the content of the script is appropriate and ready to be produced into a video to be used as a consenting tool for parents of extreme neonatal babies to view. Worked with research partners: members from the CHEO Parental Advisory Faculty Committee (PFAC), and NICU families
2. Methods Provide a clear description of the methods used	Panel members from the PFAC and two NICU families were involved. The research partners either had pediatric research experience or had a premature child. The research partners were given the script to read and provide their feedback on the content and language used. They provided their interpretations of the results by email and by phone call. The main points were collected and summarized by the researchers prior to revising the script
3. Results Outcomes- report the results	Research partners reviewed the script based on their own clinical trial experience with consent, and having sick children in the NICU
4. Discussion Outcomes-positive and negative outcomes	The involvement with the research partners was an effective in contributing to the understanding of factors influencing the readability and information presented in the script. Especially, they identified the importance of having the doctor narrate the video, reducing complex words used in the script, emphasizing more on the safety of the cells and the ethics rather than the production of the cells. They also suggested including a case study of a child with BPD to resonate with parents in the NICU.
5. Reflection	The members were able to provide insightful feedback on the script before it was finalized. One parent provided feedback over the phone while the others provided written responses. This may have limited the depth of interpretation as majority preferred to email rather than having a conversation and dis

Appendix C- Animated Video Storyboard & Video Link

<table>
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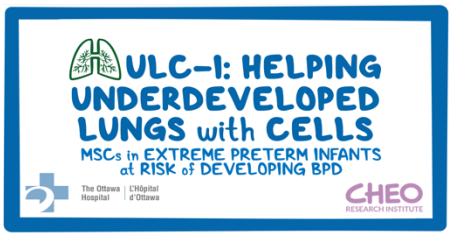
<td> 
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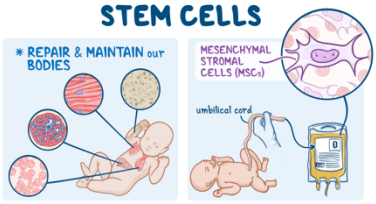
<td> 
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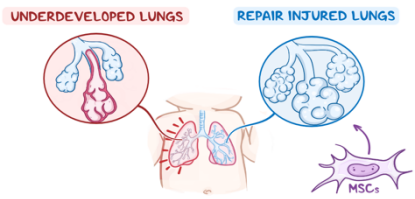
<td> 
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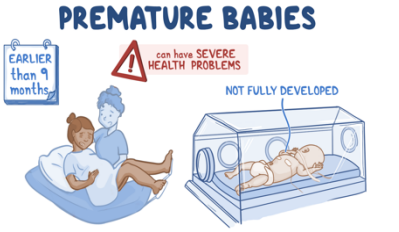
<td> 
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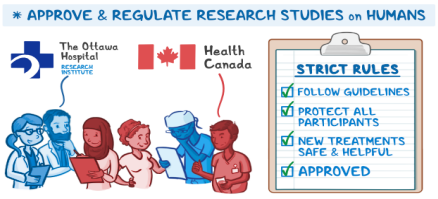
<td> 
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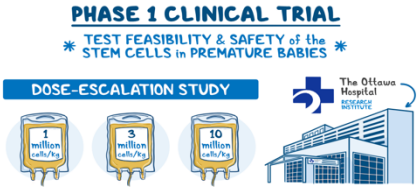
<td> 
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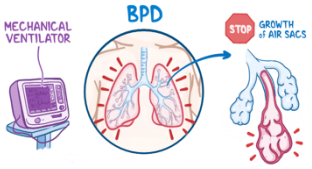
<td> 
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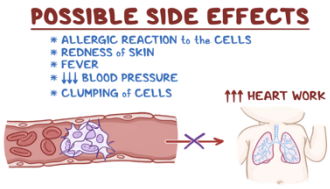
<td> 
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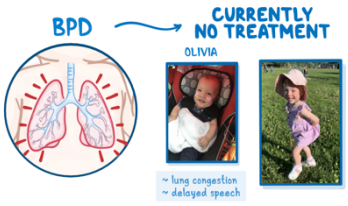
<td> 
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YouTube link of video: https://youtu.be/x5ljZqLuX6I

Appendix D- Interview Guide

Introduction

Thanks for speaking with me today. I'm Kiran, a Master's student and I'm working with Dr. Thébaud who is one of the neonatologists. My chats with parents take about an hour. If it's still ok, I will audio-record our discussion to make sure that I capture all your thoughts. Don't worry; all identifying info (your name/names of others) mentioned will be removed and replaced with a code. If you want to take a break or stop or if you wish to withdraw from the study, you are completely free to do so at any point.

I am going to discuss a hypothetical situation which involves your child participating in an interventional clinical trial and ask you some questions related to the trial conduct. There really are no right or wrong answers to the questions; I'm really just interested in your honest opinions. Any questions?

Pre-Interview

1. Have you or anyone that you know been involved in clinical research? Have you or any of your children ever been asked whether you would like to take part in a clinical trial?

This is the consent form regarding the clinical trial using stem cells to treat Bronchopulmonary Dysplasia. Have the parents read the consent form?

Having read the consent form, what are your initial reactions? Do you have any questions or concerns that are not yet answered?

2. What do you know about clinical trials? Can you tell me about how clinical trials are run?
   PROMPT: I'm interested in your views on Phase 1 trials (DOMAIN: KNOWLEDGE)

3. Have you ever heard of stem cells before? What do you think about them and how they are collected? (DOMAIN: KNOWLEDGE)

4. Have you ever heard of a disease called "Bronchopulmonary Dysplasia" before reading the consent form? (DOMAIN: KNOWLEDGE)

5. Would you ever consider enrolling your child in a stem cell trial? (DOMAIN: INTENTION)
   PROMPT: Would you like to have the information presented in another way?
   PROMPT: What additional information would you need to feel comfortable with your child participating in a trial of stem cells for BPD? (DOMAIN: BELIEFS ABOUT CONSEQUENCES AND ENVIRONMENT & RESOURCES)

6. Who would you like to hear this trial from? (DOMAIN: SOCIAL INFLUENCE)
   PROMPT: Who would you feel more comfortable hearing the trial from? Healthcare professional? Trained research assistant?

7. Is there anything about this trial that concerns you or that you can see potentially causing problems if your child took part? (DOMAIN: BELIEFS ABOUT CONSEQUENCES)
   PROMPT: What reasons might stop you from enrolling your child in a clinical trial? (DOMAIN: DEPENDS ON ANSWER)

8. Knowing what you know so far about clinical trials, how confident are you to make a decision to enroll your child in a stem cell trial? What might make you feel less confident that you could enroll them? What might help to feel more confident? (DOMAIN: BELIEFS ABOUT CAPABILITIES)
   PROMPT: How are you weighing the option to participate or not? (DOMAIN: REINFORCEMENT)

9. Would you consider enrolling your child in this trial that is intended to assess safety of treatment and not designed to improve your child's health? (DOMAIN: INTENTION)

10. Would you enrol your child in this trial if they were eligible? (DOMIAN: INTENTION)

We're developing a video to help answer some questions that parents might have when considering whether to enrol their child in the future. We'd love to show you what it look like and then ask you a few questions afterwards. Show MSC animated video

Having seen the video, what are your initial reactions? Do you have any questions or concerns that are not yet answered?

11. After watching the video, can you tell me a little bit about how clinical trials are run?
    PROMPT: The role of Health Canada and the two REBs (DOMAIN: KNOWLEDGE)
    What are your views on stem cells and its potential to treat BPD? What are your thoughts on which way they're collected? (DOMAIN: KNOWLEDGE)

12. Are you comfortable with who presented the information? What are your thoughts about the team that will run the study? (DOMAIN: SOCIAL INFLUENCE)

13. Are you able to make an informed decision with the information presented in the video? Do you need to re-watch it a second time? (DOMAIN: MEMORY, ATTENTION, DECSION MAKING)
    PROMPT: Would you like to have the information presented in another way?
    PROMPT: What additional information would you need to feel comfortable with your child participating in a trial if stem cells for BPD? (DOMAIN: BELIEFS ABOUT CONSEQUENCES AND ENVIORMNENT & RESOURCES)

14. After watching the video, how confident are you to make a decision to enrol your child in this trial? What might make you feel less confident to enrol your child in this trial? What might help you feel more confident? (DOMAIN: BELIEFS ABOUT CAPABILITIES)

15. What would motivate you to consider enrolling your child into this study? What are some of the benefits of enrolling your child in this trial? (DOMAIN: BELIEFS ABOUT CONSEQUENCES)

PROMPT: Child benefit, science benefit, society benefit, benefit of future children

16. Are there any concerns or that you can see potentially causing a problem if your child took part? (DOMAIN: BELIEFS ABOUT CONSEQUENCES)

17. When watching the video what emotions come to mind? If your child was participating in the trial, how would you feel? (DOMAIN: EMOTION)
    PROMPT: Worried, nervous, inspired, anxious, stressed, satisfaction

18. After watching the video, is there anything that is still a barrier to you for enrolling your child in a stem cell trial for BPD that you haven't mentioned that didn't come into mind? (DOMAIN: DEPENDS ON ANSWER)
    PROMT: What are the biggest concerns about enrolling your child into this trial?
    PROMPT: Do you think the benefits outweigh the risks of participating? (DOMAIN: OPTIMISM)

19. Whose opinion is important to you when considering whether to enrol your child in this trial? Would you like to show the video to others? Who would you consult with? (DOMAIN: SOCIAL INFLUENCE)
    PROMPT: Relatives, friends, physician, nurse

20. How would enrolling your child into a stem cell trial for treating BPD fit with how you see yourself as a parent? (DOMAIN: SOCIAL ROLE AND IDENTITY)
    PROMPT: What about your role is society?
    PROMPT: What is important to you?

21. How would taking part in this trial fit alongside everything else you and your family do? (DOMAIN: GOAL)

22. Based on what you have learned about the trial, would you enrol your child?
    PROMPT: if yes, why? If no, why not? (DOMAIN: INTENTION)

The interview is over, is there anything else you would like to ask me or comment or thoughts you had that might help other parents?

Appendix E- Main Informed Consent Form for Participation in a Research Study

Study Title: Helping Underdeveloped Lungs with Cells (HULC-I): A phase I trial of Mesenchymal Stromal Cells in extreme preterm infants at risk of developing Bronchopulmonary Dysplasia

OHSN-REB Number*: insert number*

Principal Investigador: Dr. Bernard Thébaud, 613-737-8899 ext: 72610

Funder(s): Canadian Institute of Health Research and Ottawa Institute of Regenerative Medicine

Emergency Contact Number (24 hours / 7 days a week): 613-737-8899 ext. 0 request page# 594 2556

INTRODUCTION

You and your infant are being invited to participate in a clinical trial/study (a type of study that involves research). You are invited to participate in this study because your child was born before 28 weeks of gestational age and is at high risk of developing bronchopulmonary dysplasia (BPD), a type of chronic lung disease. This consent form provides you with information to help you make an informed choice. Please read this document carefully and ask any questions you may have. All your questions should be answered to your satisfaction before you decide whether to participate in this research study.

Please take your time in making your decision. You may find it helpful to discuss it with your friends and family.

Taking part in this study is voluntary. You have the option to not participate at all or you may choose to leave the study at any time. Whatever you choose, it will not affect the usual medical care that you receive outside the study.

IS THERE A CONFLICT OF INTEREST?

There are no conflicts of interest to declare related to this study.

WHAT IS THE BACKGROUND INFORMATION FOR THIS STUDY?

Babies who are born very prematurely are often born before their lungs have fully developed. As a result, they may need the help of a mechanical ventilator so that their body can get the oxygen it needs to continue to grow and survive. Unfortunately, this life-saving machine can also cause damage to the lungs that leads to chronic lung disease called bronchopulmonary dysplasia, or BPD. BPD has long-term respiratory and neurological consequences that go beyond childhood. To date, there is no specific treatment for BPD.

There is laboratory evidence showing that stem cells may be effective in the prevention and treatment of BPD. Stem cells are a special group of cells that can divide and develop into different cell types. These cells are important for organ development, repair and maintenance. Work by our laboratory has shown that a specific type of stem cell, called mesenchymal stromal cells (MSCs), may be a promising new treatment for babies at risk of BPD. Our research has shown that MSCs from the umbilical cord tissue work particularly well at protecting the lungs from the injury caused by oxygen and mechanical ventilators.
The umbilical cord MSC product (which we will simply refer to as the stem cell product) that we will be testing in this study is considered investigational. Health Canada, the regulatory body that oversees the use of stem cell products in Canada, has approved the use of umbilical cord MSCs for this research study. Health Canada has not approved the sale or routine use of the stem cell product to treat babies with BPD.

WHY IS THIS STUDY BEING DONE?

The purpose of this Phase 1 study is to learn more about the safety of stem cells, the feasibility of running a stem cell clinical study, and what effects this stem cell product might have on your infant and BPD. We are also looking to find the highest dose of stem cells that can be tolerated without causing severe side effects. Lastly, we are trying to find out if this stem cell product will reduce the risk of developing BPD in premature infants, but this question may be difficult to answer in this first study because of the small number of babies that will be enrolled. This is the first time these stem cells have been tested in infants. Whether this stem cell product helps infants at risk of BPD is unknown. The results of this study may help us find the safest and most helpful dose of the stem cell product to give to infants to prevent BPD.

WHAT OTHER CHOICES ARE THERE?

You can choose not to participate in this study. If you choose not to participate, you will still receive standard of care treatments. Your study doctor will discuss these options with you.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

It is anticipated that 9 infants will take part in this study at the Ottawa Hospital, General Campus. Depending on the observed safety, it is possible that as few as 1 and as many as 12 infants will take part in this study.

WHAT WILL HAPPEN DURING THIS STUDY?

We will test three doses of stem cells in this study. As shown in the table below, up to 3 infants will be enrolled into each dose group. Each group will use a different dose of stem cells. Infants enrolled in Group A will receive the lowest dose and infants enrolled in Group C will receive the highest dose. The first 3 infants to join the study will be enrolled in Group A, the following 3 will be enrolled in Group B, and the last 3 infants will be enrolled in Group C. Enrolment into Group A must be completed before any infants may be enrolled into Group B. During this time, safety information will be reviewed to confirm that the stem cell dose used in Group A is safe before proceeding to the next higher doses. The same safety review process will be followed after enrolment of Group B is complete and before enrolment of any infants into Group C begins. If one of the infants experiences a health issue in Group B, an additional 3 infants may be enrolled into Group A to provide further safety measurements as the low dose. If one of the infants experiences a health issue in Group C, as additional 3 infants may be enrolled into Group B to provide further safety measurements at the mid dose.

If you decide to participate and after signing this form, you will be assigned into one of the groups described below. As mentioned, the group you are assigned to will be determined by the time of enrolment. You will be told which group you are in.

Group	Stem cell Dose	Number of participants	Infusion duration
Group A:	1.0 million cells/kg	up to 6	15 minutes
Group B:	3.0 million cells/kg	up to 6	15 minutes
Group C:	10 million cells/kg	up to 3	15 minutes

WHAT IS THE STUDY INTERVENTION?

If you agree to participate in this study, depending on the time of enrolment, you will be assigned to one of the three groups. Your infant will receive the stem cell product, which is MSCs taken from a donated human umbilical cord. The umbilical cord comes from a healthy term baby. All umbilical cord donors undergo rigorous safety screening to ensure the donated umbilical cord, and the cells that come from that cord, are safe from any infectious diseases. If you would like more information about the donor screening, please go to the following link https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-

therapies/regulatory-initiatives/cells-tissues-organs/guidance-document-safety-human-cells-tissues-organs-transplantation/document.html#a2.6

The stem cells taken from the donated umbilical cord will be processed in a laboratory qualified to prepare the stem cell product. Before the stem cell product can be used in this study, it must first pass a series of quality and safety testing.

The procedure (intravenous I.V. injection of the stem cell product) will take 15 minutes. If your infants does not already have an I.V., an I.V. will be inserted. Your infant will receive only 1 administration of the cells after consent is obtained.

Infants who are in Group A will receive a one-time dose of 1 million cells per kilogram of body weight (million cells/kg) via your infant's I.V. line and administered under the supervision of a study physician.

Infants who are in Group B will receive a one-time dose of 3 million cells per kilogram of body weight (million cells/kg) via your infant's I.V. line and administered under the supervision of a study physician.

Infants who are in Group C will receive a one-time dose of 10 million cells per kilogram of body weight (million cells/kg) via your infant's I.V. line and administered under the supervision of a study physician.

WHAT ARE THE STUDY PROCEDURES?

Data Collection

The researchers will collect information from your infant's medical chart from admission until the end of patient follow-up and enter this information into an electronic database. Please talk to the research team if there is information that you do not feel comfortable sharing.

Blood Sample Collection

2 blood samples from your infant will be taken by the infant's nurse. These samples will be taken at the time of participant enrolment and 72-96 hours after the stem cell product injection to see if there is a difference in inflammation before and after stem cell injection. This will help us understand how the stem cells work. This test is considered experimental. These blood samples will be drawn at the same time as routine blood work and require a minimal amount of blood (100μl or 2 drops). Hereditary genetic testing will not be done on these samples.

Reports about any research tests done with your infant's blood samples will not be given to you or other health care providers. These reports will not be put in your child's medical record.

Tracheal Aspirate Collection

2 tracheal aspirate samples from your infant will be taken by the baby's nurse to obtain baseline of lung biomarkers in neonates. These samples will be taken at enrolment and 72-96 hours after the first suctioning of the airways. The tracheal aspirate samples will be collected at the same

time as the clinically indicated suctioning of the airways. No suctioning will be done for the sole purpose of this study and collection of tracheal aspirates will not be done.

Parental Interview

We will conduct 1-to-1 interviews with parents after enrolment at The Ottawa Hospital. Once consent is obtained, we will schedule a time to conduct the interview. The interview is to evaluate the effectiveness of an animated information video. You will be asked a series of questions to assess whether the video addresses any remaining informational needs regarding BPD, Phase 1 clinical trials and MSC/stem cells and whether it clarified additional support available to help your decision-making process. The interviews will be around an hour long and will be audio-recorded. The information you provide is for research purposes only. Some of the questions are personal and you can choose not to answer if you wish.

Targeted Neonatal Echocardiography (TnEcho)

A physician who is a part of the study will be performing a TnEcho, an ultrasound used to obtain measurements of the blood pressure in the lungs. The data collected will be used to compare if there are any effects to the lungs and blood circulation before and after cell injection. The TnEcho will be done at enrolment (unless done 2 days prior) to have a baseline measurement, and then at 48 hours, 28 days and 36 weeks corrected gestational age. This non-invasive procedure is part of standard of care in preterm infants. For the purpose of this study, the measurements at enrolment and 48 hours after stem cell injection were added specifically to ensure we capture any effect of the stem cell injection.

Patient Follow-up

When your child reaches the age of 18-24 months (corrected gestational age), your child will be evaluated at the follow-up clinic for premature infants (as a standard of care; all infants born under 29 weeks in the Ottawa area are assessed at this clinic) at CHEO. At this visit, an assessment of the motor, language, cognitive and physical development, vision, hearing and general health status will be performed. In addition to this standard of care appointment we would like to perform a neurodevelopmental assessment as part of the study follow-up. This will take about 60-90 minutes.

How will blood and tracheal aspirate samples be identified?

To protect the identity of your infant, the information that will be on the samples will be limited to a unique participation identification number.

Despite protections being in place, there is a risk of unintentional release of information. Due to technological advances in genetics, there may be a risk that the genetic information in the samples could be linked back to you.

Can I withdraw these samples?

If you no longer want your samples to be used in this research, you should tell the research team. If tests have already been done on your samples, it will not be possible to withdraw those results. However, no further testing will be done.

WHAT ARE THE RESPONSIBILITIES OF STUDY PARTICIPANTS?

If you choose to participate in this study, you will be expected to:

- Tell the study doctor if you are thinking about having your infant participate in another research study
- Provide updated contact information for the 10-year Long-Term Patient Safety Follow-up phone call and e-mail

HOW LONG WILL PARTICIPANTS BE IN THE STUDY?

Participants will be enrolled between the first 7 to 21 days of life and your infant will be followed until 40 weeks corrected gestational age or until they are discharged (whichever comes first). Once your infant is 18-24 months corrected age, arrangements will be made to assess your child's cognitive, language, and motor skills. In addition, information on additional motor, vision and hearing skills will be gathered. Any information from this assessment will be followed at the CHEO Neonatal Follow-up Clinic. After completing this visit to the follow-up clinic, you will be contacted once a year for 10 years so that we can check up on your child's overall health.

CAN PARTICIPANTS CHOOSE TO LEAVE THE STUDY?

You can choose to end your infant's participation in this research (called withdrawal) at any time without having to provide a reason and without any impact to your infant's care. If you choose to withdraw from the study, you are encouraged to contact the research team.

You may withdraw your permission to use information that was collected about you and your infant for this study at any time by informing the study research team. However, this would also mean that you withdraw from the study. Information and blood and tracheal aspirate sample results that were recorded before you withdrew will be used by the research team for the purposes of the study, but no further information will be collected after you withdraw your permission.

CAN PARTICIPATION IN THIS STUDY END EARLY?

The study doctor may stop your infant's participation in the study early, and without your consent, for reasons such as:

- Your infant is unable to tolerate the study intervention
- New information shows that the study intervention is no longer in your infant's best interest
- The study doctor no longer feels this is the best option for your infant
- The Regulatory Authority/ies (for example, Health Canada), the Ottawa Health Science Network Research Ethics Board or the CHEO Research Ethics Board withdraw permission for this study to continue

If your infant is removed from this study, the study doctor will discuss the reasons with you and plans will be made for your infant's continued care outside of the study.

WHAT ARE THE RISKS OR HARMS OF PARTICIPATING IN THIS STUDY?

You may experience side effects from participating in this study. Some side effects are known and are listed below, but there may be other side effects that are not expected. You should discuss these with the study doctor.

This stem cell product is in an early phase of development and not approved by Health Canada for the treatment of lung disease in infants. A similar umbilical cord stem cell product manufactured in our facility was used in laboratory experiments. There were no severe adverse events detected in these studies.

There may be side effects in infants that we do not know about yet. Although the use of similar stem cell products in clinical trials revealed no major safety concerns, there are still some possible risks associated with the use of this stem cell product:

1. If the cells clump together after being injected, this can cause a blockage in your baby's blood vessels.
2. Your baby may experience a fever after the stem cells have been administered.
3. Your baby may experience an allergic reaction to the stem cells.
4. Your baby may experience some bruising around the injection site.
5. Your baby may get an infection as a result of the stem cell injection.

The study doctor will watch your infant closely to address any concerns. If necessary, other medication will be given to your infant to treat the side effects or make them more tolerable. Many side effects go away shortly after the study intervention is stopped, but in some cases side effects can be serious, long-lasting, permanent, or may even cause death.

It is possible that other medications or vitamins can interact with the study intervention. This can result in either the intervention not working as expected or result in severe side effects.

Blood sampling obtained is equal to two drops of blood. There is no expected risk to your baby except for minor bruising. Tracheal aspirate suctioning is routinely performed and necessary to clear the airways in intubated patients. The tracheal aspirate samples will be collected during routine clinical suctioning (no suctioning for the study alone).

The TnEcho is a common procedure performed as part of standard of care for babies less than 29 weeks gestation and no side effects or risks have been reported.

While there is nothing particularly risky about the interviews, you might find the process tiring. You do not have to answer any questions that make you feel uncomfortable.

Risk of Insurability:
There is a possibility that participation in research may affect your insurability under certain insurance policies.

WHAT ARE THE BENEFITS OF PARTICIPATING IN THIS STUDY?

You may not receive any direct benefit participating in this study. Your participation may allow the researchers to know the safe effective dose of the stem cell product, and we hope the information learned in this study will help other infants with BPD in the future.

HOW WILL PARTICIPANT INFORMATION BE KEPT CONFIDENTIAL?

If you decide to participate in this study, the research team will only collect the information they need for this study. All study information collected during your participation in this study will be identified with a unique study number, and will not contain information that identifies you, such as your name, address, etc. The link between your unique study number and your name and contact information will be stored securely and separate from your study records.

Records identifying you will be kept confidential and, to the extent permitted by the applicable laws, will not be disclosed or made publicly available, except as described in this consent document.

Authorized representatives of the following organizations may look at your original (identifiable) medical records at the site where these records are held, to check that the information collected for the study is correct and follows proper laws and guidelines.

The Ottawa Health Science Network Research Ethics Board and CHEO Ethics Board who oversees the ethical conduct of this study.
Ottawa Hospital Research Institute or Ottawa Heart Institute Research Corporation and the CHEO Research institute, to oversee the conduct of research at this location.
Health Canada (because they oversee the use of stem cell products in Canada)

Information that is collected about your infant for the study (called study data) may also be sent to the organizations listed above. Your name, address, email, or other information that may directly identify you will not be used. The records received by these organizations may contain your disclosed identifiers e.g., participant code, pseudo-initials, sex, and partial date of birth (month and year). Blood samples collected for this study will be stored in a secured facility within the Ottawa Hospital, General Campus. Blood samples will be kept for the duration of the study (approximately 2 years). The Ottawa Hospital Research Institute Data Management Services Group will also receive your study data. If the results of this study are published, your identity will remain confidential. It is expected that the information collected during this study will be used in analyses and will be published/ presented to the scientific community at meetings and in journals. Even though the likelihood that someone may identify you from the study data is very small, it can never be completely eliminated. A copy of the consent form that you sign to enter the study may be included in your infant's medical record/hospital chart. Research records will be kept for 25 years, after this time they will be destroyed.

WILL FAMILY DOCTORS/HEALTH CARE PROVIDERS KNOW WHO IS PARTICIPATING IN THIS STUDY?

Your family doctor/health care provider will not be informed by the study team that you are taking part in the study. You can choose to let your family doctor/health care provider know, if you like.

WILL INFORMATION ABOUT THIS STUDY BE AVAILABLE ONLINE?

A description of this clinical trial/study will be available on http://www.clinicaltrials.gov. This website will not include information that can identify you. You can search this website at any time.

WHAT IS THE COST TO PARTICIPANTS?

Participation in this study will not involve any additional costs to you or your private health care insurance.

ARE STUDY PARTICIPANTS PAID TO BE IN THIS STUDY?

If you decide to participate in this study, at the neurodevelopment appointment you will receive $50.00 for study related expenses such as parking cost, gas, and meals. In the case of research-related side effects or injury, medical care will continue to be provided to your infant as per standard of care.

WHAT ARE THE RIGHTS OF PARTICIPANTS IN A RESEARCH STUDY?

You will be told, in a timely manner, about new information that may be relevant to your willingness to stay in this study. You have the right to be informed of the results of this study once the entire study is complete. If you would like to be informed of the results of this study, please contact the study research team. Your rights to privacy are legally protected by federal and provincial laws that require safeguards to ensure that your privacy is respected. By signing this form you do not give up any of your legal rights against the study doctor or involved institutions for compensation, nor does this form relieve the study doctor or their agents of their legal and professional responsibilities.

You will be given a copy of this signed and dated consent form prior to participating in this study.

WHAT IF RESEARCHERS DISCOVER SOMETHING ABOUT A RESEARCH PARTICIPANT?

During the study, the researchers may learn something about your infant that they didn't expect. If any new clinically important information about your health is obtained as a result of your participation in this study, you will be given the opportunity to decide whether you wish to be made aware of that information.

WHOM DO PARTICIPANTS CONTACT FOR QUESTIONS?

If you have questions about taking part in this study, or if you suffer a research-related injury, you can talk to your study doctor, or the doctor who oversees the study at this institution. That person is:

Dr. Bernard Thébaud	613-737-8899 ext: 72610
Principal Investigator Name	Telephone

If you have questions about your rights as a participant or about ethical issues related to this study, you can talk to someone who is not involved in the study at all. Please contact The Ottawa Health Science Network Research Ethics Board, Chairperson at 613-798-5555 extension 16719 or the CHEO Research Ethics Board at 613-737-7600 extension 3272.

Appendix F- Summary of belief statements and sample quotes from participants assigned to domains identified as relevant

Domain	Subtheme	Belief statement	Frequency (out of 14) (n=%)	Sample quote
Knowledge	Existing knowledge about stem cells	I am somewhat aware of stem cells	8 (57)	"I know some information about stem cells from documentaries and you see the potential it has to correct organs, so I know that there is potential for it"-Participant 11
		I am unaware of stem cells	6 (43)	"I was coming in with very little information. There is a bit of curiosity there."- Participant 10
	Knowledge about stem cells after reaching ICF and video	I would like to know more about toxicity, and expected outcomes	9 (62)	"Like this trial is a Phase 1 trial, I would want to know the expected outcomes. Explain what would happen if you or you got the results they wanted or didn't get."- Participant 3
		I would like to know more about the efficacy of the cells	1 (0.07)	"I'm not really sure I understand how you identify the efficacy of the cells?"- Participant 2
		I would like to know more about the preclinical data after reading ICF	7 (50)	"The only thing I noticed was with the dosage count, 1,5, and 10 million. It would be nice to have background on those numbers. Like why these numbers? What's the difference between each dosage? It's quite a big difference."- Participant A03 "I know it brought up the fact that preclinical research was safe but not enough in the paper justifying how safe it is"- Participant A05
		I would like to know more about the preclinical data after watching the video	6 (43)	"I didn't really see too much of like what has happened to get to this point to test these cells in babies. That was a big question. So, I didn't see a whole lot of context about what has happened to get the confidence to proceed with that next steps"-Participant A04
	Knowledge of BPD	I have heard of BPD before	4 (29)	"I'm part of like a micro preemie Facebook group and so that's just mentioned occasionally." – Participant 2
		I have never heard of BPD	9 (62)	"Prior to reading the consent form, no. I still don't really know about it. I couldn't give you a straight answer."- Participant A03
	Existing knowledge of clinical trials prior to reading ICF and watching video	I am aware of clinical trials and the different phases	4 (29)	"Typically, there's like years of research for clinical studies and there's certain criteria that they're looking for, and then there's usually like a defined period and observe the results."- Participant 3
		I know trials help advance clinical care	5 (36)	"My understanding would be they would be to ensure that whatever drug would be given in the future, would be safe." Participant 2
		I am unaware of clinical trials	4 (29)	"No, I do not know… first time for me hearing about this"- Participant 12

	Knowledge of study procedures	There needs to be a clear understanding of the patient population in the video	4 (29)	"Target demographic as well, I know everything was just described in months, but like my son is 24 weeks (GA). I had another preemie before, but she was 35 weeks (GA) which seems like a different ball game entirely. But just thinking about like for me and I think for other people who are in the same type of situation, you're thinking about everything in weeks not months"- Participant 2
Environmental context and resources	The timing of approach	The logistical factors (timing/ location) will influence my decision to participate	5 (36)	"I'm just thinking back to when we were approached just for this initial yeah phase. It was at a time where there was lots of ups and downs so it was very difficult for us to make the decision of whether it would be good timing"- Participant 1
		Approach should reflect how the baby is doing	2 (14)	"I think depending on parents and level of comfort and what the state of the baby is in, I think the approach should reflect the baby and maybe the attending neonatologists should be there during the approach."-Participant 3
	Access to information	It is important to have access to comprehensive information (after reading the ICF and watching the video)	11 (79)	"Having as much information in from a variety of sources I think is helpful making any decision in this situation. I think it's an added benefit. Like I was saying having other options and considering the sensitivity that might be needed in having these conversations. I think it's great to have as many different modes of communication as possible."-Participant 10
		The two different communication methods are enough to decide	3 (21)	"You get so much documentation and pamphlets, it's overwhelming. You don't want more junk in your house. So, getting the consent form, the video and speaking to the researcher in the hospital is sufficient and easy to understand"-Participant 2
	Enabling resources	The informed consent form provided all the necessary information	11 (79)	"I thought it was lengthy, but then when I read through it, it all seemed like relevant information that would be necessary. I think as a parent you are already trying to weigh all the options of whether it would be a good fit. So being able to have as much information about all the details right off the bat, I think it's helpful. The more I read it, the more I could see why it was lengthy because it brought up other things I never even thought about"-Participant 10
		The consent for is not an ideal source of information	3 (21)	"The consent form is exaggerating a bit to be on the cautious side. I felt like video, it is a little bit different than the consent form. The consent form is more like a legal document and the video is more informational. "-Participant 1
		The video is a great source of information	8 (57)	"I'm a visual person, so I found the visuals quite helpful and less intimidating, I think as well, I could tell that the information was not to say less complex, but it was definitely accessible. Even if English wasn't my first language, I still would be able to identify and understand everything" -Participant 10

Beliefs about consequences	Side effects and safety	I am concerned about the potential side effects (after reading ICF and watching video)	9 (64)	"One complication that kind of scared me was the clumping of the cells. My understanding is you know something in your veins is never very good stuff. It could cost really cause serious complications, so my mind kind of went into the adult world with blood clots. And if that happens, how are we going to treat it? Is it a significant risk? I know there was some lines in the consent form, but it wasn't enough for me to be reassured. Like yes you will monitor the experience but like what would you do, right? It wasn't clear to me"-Participant A03 "I don't want my child to be a guinea pig. Obviously, it would to be like to benefit babies in the future and stuff but am I willing to risk my child's life to see if there is a benefit."-Participant 5
		Clarity of the expected outcomes of experimental treatment compared to standard of care	2 (14)	"I can weigh the risks of administering the stem cells to the child compared to the risks of not administering them or staying on the ventilator for a quite a bit that may lead to chronic pulmonary problems." – Participant A02
		Uncertainty with Phase 1 trials	5 (36)	"The other study that we are participating in, has 1000's of participants. This Phase 1 only had 9 and I don't want my child to be the first to receive the cells"- Participant 5
		The risks do not concern me	4 (29)	"There's always risk. You know those side effects, should my child experience issue with blood pressure and things like that. There are things that you can do to address that."- Participant A04
	Expected and unexpected outcomes	Clarity of likelihood of being diagnosed with BPD after watching the video	4 (29)	"The video could kind of scare some parents, right? Because they're like my babies on ventilation. Is this going to happen to my baby? So, like maybe making it clear like you said that this is an extreme case because that was not clear in the video"- Participant 3
		Expected outcomes of receiving the cells	8 (57)	"Information on risk involved or like worst case scenario, nothing will happen. Best case scenario we might see slight improvements, or these are the markers that we are looking for during the trial kind of thing to put me at ease. So, outcomes from the study"- Participant 10
	Treatment benefits	The trial will benefit the patient	7 (50)	"You know it's better to prevent. Like she gets older, and then you realize that you should have done that (join the study). So you take the chance to provide for a better life"- Participant 12
		The trial will benefit future children	8 (57)	"Like anything that could potentially benefit children in the future, so their parents don't have to go through as much of other NICU equipment."- Participant 3
	Long-term benefit	Advancing scientific research	7 (50)	"I want to participate in any study I could. That's how we improve and discover things. We discovered better ways to do that to heal people etc. The progress we've seen from the 70s up to now."- Participant 1
		Helping public infrastructures	1 (0.07)	"And when you think about the grand scheme of things, it's also you know public money that's being spent. So if it is something that could be preventable, everybody wins."-Participant M03
Beliefs about capabilities	Confident	I feel confident in my ability to make an informed	5 (36)	"No, I think the consent form pretty much covered all bases."- Participant 4

		decision after reading the ICF		
		I feel confident in my ability to make an informed decision after watching the video	5 (36)	"More confident than when we just read the paper. When we read just the paperwork, I think we're both kind of like pass."- Participant A05
	Somewhat confident	I am somewhat confident to decide after reading the ICF and watching the video	4 (29)	"So, when it comes to my baby, I'm definitely a little more hesitant, more hesitant than I would be for myself."-Participant A04
Goals	Motivators	Give a better quality of life for my child	5 (36)	"I would do it because we have a micro preemie who's very sick, so this situation where you want to do anything. Anything to help my baby survive"- Participant 2 "You want to prevent any negative effects, so you would want to give your child any treatment out there, like whatever to help benefit them"- Participant 11
		Advancing science and helping other parents	8 (57)	"Our goal is to improve medicine and the more kids that participate the more advance neonatal medicine will be and increasing the survival rates and the gestation they are born at."-Participant 1
Intention	Intent to participate	I intend on participating in the trial after reading the ICF	5 (36)	"I think so, I probably would."- Participant 2
		I intend on participating in the trial after reading the ICF after watching the video	10 (71)	"If I was presented with video alone, I'd be more likely to say yes. If I'm presented with the consent form alone, most likely I would say no" Participant 1
	Intent to not to participate	I do not intend to participate after reading the ICF	2 (14)	"Unless the wording of the consent form changed because it is 100% accurate. Like their exaggerating a bit to be on the cautious side, I would not participate."- Participant 11
		I do not intend to participate after watching the video	2 (4)	"Knowing what we know I would say no cause there is no benefits and more risks. We already have pregnancies that didn't work so I wouldn't take the chance"-Participant 12
	Conditional intent	I would rather participate in an efficacy trial rather than a safety trial	3 (21)	"If it's solely just to test the safety of this procedure. I would say no to the trial, I am not sure what would really happen to my child"- Participant A03
		I would only participate if there were no other option	4 (29)	"Maybe if it was a life of death situation maybe I'll reconsider"- Participant 5

Skills	Finding additional information	I know how to find information on stem cell research	3 (21)	"I come from a scientific background. I know how to search on my own and learn about stem cells and its potential"-Participant 1
Social Influence	Perception of the video	The PI in the video provides social support	7 (50)	"Definitely having him in the video you can see and hear the actual person doing the study."-Participant 4
		I would want to meet the PI in person	3 (21)	"Dr. Thébaud narrating the video does not really change a lot for me. Whether it's him or somebody else, unless I can talk to him face to face, I'm going to actually be more comforted because I know because the video is general"- Participant 1
		Having ethics in the video is great	8 (57)	"Knowing that there's an Ethics Committee and the extensive vetting that goes through this, at least here in Canada before things get put into place. Knowing that really helps"-Participant 10
		The video advocates to prompt more questions	5 (36)	"I think from the video it prompts questions. I think it is a good opportunity for a discussion without it getting too complex."-Participant A03
		The case study helps with relatability	6 (43)	"I think initially, hearing or seeing Olivia's story was helpful in terms of relatability. You know, hearing a story with very similar circumstances as to you." Participant 10
	Neonatologists and bedside nurses	I trust the attending neonatologist and would want their opinion	6 (43)	"For me I would reach out to my baby's doctor. If they feel alright, I would be more inclined to participant"-Participant 4
		I trust the bedside and would want their opinion	6 (43)	"Practically speaking, like day-to-day, we see our nurses 100% more often than doctors, so I'm like you might get a couple of check-ins per week with a doctor, but the nurses would probably be more important."-Participant 2
	Family and friends	My partner's opinion only matters	7 (50)	"I would need to talk to my wife first, but it would be a very long conversation, but I would."-Participant A03
		I would seek advice from family members	1 (0.07)	"I would discuss this with my mother in-law. In the other study we asked for her opinion"-Participant 5
		I would speak to my doctor friends	2 (14)	"We have a doctor that we are close to, so we will bring this to his attention."- Participant 12
	Research staff	I would want trial information from a research staff	5 (36)	"I think it's fine with one of the research assistants providing information but making the neonatologists available for any additional questions if necessary."-Participant 3
Emotion	Positive and hopeful	I felt inspired after watching the video	5 (36)	"It's definitely hard going through all of that. So anything to really help make it right, makes me feel better"-Participant 11
	Anxious	I felt anxious after reading the ICF	1 (0.07)	"Reading about the blood sample collection and then you have tracheal aspirate collection and I think that it may be a scary term for parents."- Participant A04
		I felt anxious after watching the video	6 (43)	"I was worried after seeing Olivia, I did not want my baby to end up like that."-Participant 8
	Mixed emotions	I have mixed feelings about this trial	6 (43)	"It is very emotionally driven, and it worries me a bit about all of the unknowns and if it might help my baby"-A03

Memory, attention and decision process making	Cognitive recall	After watching the video, I was able to recall the study information	8 (57)	"Personally, I am able to recall the information a lot better. I know there are 3 groups and each group received different dosages"- Participant 11
	Factors influencing decisions	I would need to have a conversation with health care professionals	8 (57)	"I think I would be more inclined to consider it. Yeah, I'm still not 100%. We still need to sit down with the doctors and stuff like that, but like this is very good"- Participant 10
		Substitute decision maker	1 (0.07)	"Because it's our child who can't consent herself. You know, for us, it might not seem like a lot in terms of blood samples and aspirates. You don't know how she feels about it. So, it's a little bit interesting to be given consent or offering consent on behalf of someone else who can't confirm whether they're interested."- Participant 10
		Weighing out the positive versus the negatives	5 (36)	"That you know if it were like, oh we have this new medicine that we want to try. I would be way more hesitant. In my mind there is a difference with stem cells and medicine. More comfortable with stem cells."-Participant A03
Optimism	Optimistic	I would expect more good things than bad	5 (36)	"Any treatment that we have now. Somebody studied somewhere so if the risk is minimized and the negative side is, you know outweighs the positive side I would be more curious about it but right now it seems fine to me"- Participant 11
		The treatment is promising	7 (50)	"You all are doing is very good, so I'm impressed. I'm impressed with the new treatment"-Participant 9
Reinforcement	Previous clinical trial experience	I have experience with clinical trials	8 (57)	"The lactoferrin study in the NICU had no fatality. So that's why I consented to that trial. There were 2000 babies already in the study so there's proof that it works. That is why we consented"- Participant 5
	Follow-up incentives	The follow-up aided in my decision making	2 (14)	"Incentive of having the 24 month follow up, they're going to assess their neurological development and all of that. It really interests us and kind of knowing more information that like not a lot of people would have the opportunity to"- Participant A05
Social/ Professional Role and Identity	Values and ethics	I do not have any religious or moral qualms about stem cell therapies	1 (0.07)	"I know people have problems with the harvesting of the cells. I know some religious groups find it questionable, I don't. I just think it's just the process of collecting anything else in the human body."- Participant 3
	Personality and identity	My role is society	2 (14)	"I feel for me it is my duty to participate in research. This is how we evolve medicine."– Participant A03
		My role as a parent	5 (36)	"As a parent you would do anything for your child. So defiantly this would be a good decision."-Participant A02

Appendix G- Subthemes and Belief Statements

Most Relevant Domains

The most relevant domains were identified based on the criteria outlined by Atkins *et al*. (2017). Relevant domains were chosen based on the frequency with which beliefs and themes appeared in each domain, the presence of conflicting beliefs, and perceived relevance to the target behavior.

Key domains for the participant interviews were knowledge, social influence, beliefs about consequences, goals, environmental context and resources, reinforcement, intention and memory, attention and decision-making.

Domain	**Number of participants represented**	**Total number of instances coded to domain**
Nature of behaviour	0	0
Optimism	10	17
Skills	3	3
Behaviour regulation	0	0
Emotion	12	23
Social and professional role and identity	6	11
Memory, attention and decision making	11	37
Reinforcement	9	15
Knowledge	13	123
Environmental context and resources	13	45
Beliefs about consequences	13	79
Beliefs about capabilities	11	20
Goals	11	11
Intention	13	58
Social influence	13	91

Optimism
***N*=10**

Participants were asked about how optimistic they were about the new treatment. Five participants indicated that they would expect more good things than bad. Parents described the benefits of the treatment do outweigh the risk. Seven participants did mention that they see the treatment promising and the potential of this treatment being part of standard of care practices.

> R: Any treatment that we have now. Somebody studied somewhere so if the risk is minimized and the negative side is, you know outweighs the positive side I would be more curious about it but right now it seems fine to me
> *Participant #11*

> R: I think it's wicked! It's very interesting. It is a huge scientific cornerstone into a lot of modern research and a lot of modern treatments. So, I think it's incredible to see this as being a potential treatment option
> *Participant #A04*

Overall, parents were optimistic about the treatment and excited to see what comes about from this trial

Skills
***N*=3**

Three participants mentioned that if they decide to enroll in this trial, they will use their skills to search for more information to help with their decision-making process. They described doing Google searches and reading research articles where some ways for them to find information.

> R: I come from a scientific background. I know how to search on my own and learn about stem cells and its potential
> *Participant #1*

Emotion
***N* = 12**

When asked how they felt about the video, five participants mentioned being inspired about the trial. Many mentioned feeling excited and hopeful about the potential this trial may have.

> R: It's hard going through all of that. So anything to really help make it right, makes me feel better
> *Participant #11*

However, six parents did mention that they felt anxious after viewing the video, noting the case study made them feel sympathetic towards the parents as well as putting into perspective this might happen to their baby

> R: I was worried after seeing Olivia, I did not want my baby to end up like that
> *Participant #8*

One parent also mentioned that after reading the consent form they had overwhelming feeling of the amount of sample collections that would occur if they participated in the trial

R: Reading about the blood sample collection and then you have tracheal aspirate collection and I think that it may be a scary term for parents
Participant #A04

Many participants (n = 6) also described feeling mixed emotions of feeling hopeful and positive but also fearful and nervous. One participant described that participating in the trial will be emotionally driven

R: It is very emotionally driven, and it worries me a bit about all of the unknowns and if it might help my baby
Participant #A03

Social, Professional Role and Identity

***N* = 6**

When discussing the stem cell treatment, one parent did mention that the collection of stem cells from donors was not a conflict of his religious beliefs. He mentioned it was a technique to collect the cells.

R: I know people have problems with the harvesting of the cells. I know some religious groups find it questionable, I don't. I just think it's just the process of collecting anything else in the human body
Participant #3

Another parent mentioned they preferred immunotherapies over chemical ones, since it seemed more natural.

R: To me they are promising. To me, there's something you know, natural, as opposed to a synthetic drug.
Participant #1

Seven participants also mentioned aspects of their identity that may influence their decision to participate in a stem cell trial. Two mentioned their role in society was part of their identity and drew connection to their willingness to evolve medicine.

R: I feel for me it is my duty to participate in research. This is how we evolve medicine.
Participant #A03

Other (n = 5) participants discussed how deciding to enroll in this trial reflects on how they perceive themselves as parents. All stated they would do anything to help their child from suffering for this disease.

R: As a parent you would do anything for your child. So defiantly this would be a good decision
Participant #A02

Memory, Attention and Decision Making

***N*= 11**

Participants discussed additional factors that contribute to their decision making including the ability to recall study information after watching the video (n=8). This is important to prevent cognitive overload and allow parents to make an informed decision.

> R: Personally, I can recall the information a lot better. I know there are 3 groups and each group received different dosages
> *Participant #11*

Participants also discussed how important it is to have a conversational component in addition to the study documents given. The ability to discuss the study and answer questions will help with their decision making.

> R: I think I would be more inclined to consider it. Yeah, I'm still not 100%. We still need to sit down with the doctors and stuff like that, but like this is very good
> *Participant #10*

One parent also mentioned being conflicted to decide on their child's behalf although they have no say with the trial participation

> R: Because it's our child who can't consent herself. You know, for us, it might not seem like a lot in terms of blood samples and aspirates. You don't know how she feels about it. So it's a little bit interesting to be given consent or offering consent on behalf of someone else who can't confirm whether they're interested
> *Participant #10*

Reinforcement

***N*= 9**

A few participants discussed how past experiences with clinical trials influenced their decision making (n=8). Few parents were aware of other NICU studies before being approached to consent for this study and compared the studies. One parent mentioned the difference in the samples size the and the hesitancy he had while deciding to consent to the trial or not.

> R: The lactoferrin study in the NICU had no fatality. So that's why I consented to that trial. There were 2000 babies already in the study so there's proof that it works. That is why we consented
> *Participant #5*

Two participants mentioned after reading the ICF the follow-up component influenced their decision making as it was an additional assessment that is not part of standard of care practices.

> R: Incentive of having the 24 month follow up, they're going to assess their neurological development and all of that. It really interests us and kind of knowing more information that like not a lot of people would have the opportunity to
> *Participant #A05*

Knowledge

***N* = 13**

Trials

Participants were asked what they knew about clinical trials. Responses demonstrated a range of knowledge with some knowing about some aspects of clinical trials (n = 5) and others stating they knew very little (n = 4). Few participants (n = 4) indicated knowing that clinical trials had various phases and the end goal was to help improve medical care.

R: Typically phase one trials means it's very exploratory. It's in the early stages of understanding the effectiveness, and conclusions
Participant #3

R1: Clinical trials are usually the end of the road. It's a long process to reach that stage. Research has been done and you have a clear vision of where you want to go, and you want to test out the hypothesis was right. We have some expectations of how it will go on and we are coming into an end of a very long process. That is my understanding of clinical trials.
Participant #A03

Stem Cell Therapy

When asked about their familiarity with stem cells, participants similarly indicated a range of knowledge. Some (n = 8) indicated having heard about stem cells in school, and media outlets such as news and documentaries. While others reported never hearing about stem cells before being asked to participate in this trial (n = 6). Descriptions of stem cells were often brief and tentative. However, five were aware of the regenerative potential of the cells and the perceived benefits.

R: Well, stem cells could be universal, and they could be applied to a whole bunch of areas in the body. We're still understanding it. We're not sure how to utilize it to its full potential.
Participant #5

Regardless of how much participants already knew about stem cells, after reading the consent form and watching the animated video, most (n=9) expressed the desire to know more about the risks and the expected outcomes of the cells. One parent mentioned understanding the efficacy of the cells. After reading the ICF, many (n=7) mentioned understanding the preclinical data including the dosage of the cells as well as the safety of the cells. After watching the video, the same concern was voiced by six participants.

R1: Yeah, something to explain like what the overall expectations from the study and trying to show the hope with the treatment as well.
Participant #3

R2: The only thing I noticed was with the dosage count, 1,5, and 10 million. It would be nice to have background on those numbers. Like why these numbers? What's the difference between each dosage? It's quite a big difference
Participant #5

R3: I didn't really see too much of like what has happened to get to this point to test these cells in babies. That was a big question. So, I didn't see a whole lot of contexts about what has happened to get the confidence to proceed with that next step
Participant #A04

Bronchopulmonary dysplasia

Prior to being asked to participate in this observational study, only few had limited knowledge of BPD. The participants either heard of this disease from their doctors or support networks they have joined. Majority (n=9) mentioned this was the first-time hearing about this disease and wanting more information of the disease.

R: I'm part of like a micro preemie Facebook group and so that's just mentioned occasionally.
Participant #2

R1: Prior to reading the consent form, no. I still don't really know about it. I couldn't give you a straight answer.
Participant #A03

Patient population
After watching the video, 4 parents mentioned that having the patient population described in weeks rather than months will help improve parents understanding.

R: Target demographic as well, I know everything was just described in months, but like my son is 24 weeks. I had another preemie before, but she was 35 weeks which seems like a different ball game entirely. But just thinking about like for me and I think for other people who are in the same type of situation you're thinking about everything in weeks not months
Participant #2

This suggests that having the demographic explained in weeks will make it more relatable to parents.

Environmental Context and Resources
***N* = 11**

Timing of approach
Many parents mentioned that the timing of approach was important. Five parents mentioned that researchers should wait few weeks before approaching since they are in a new environment and focused on their infant's health. Two voiced out that the timing should reflect on how well the baby is doing.

R: I'm just thinking back to when we were approached just for this initial yeah phase. It was at a time where there was lots of ups and downs so it was very difficult for us to make the decision of whether it would be good timing
Participant #1

This suggest that we need to take into consideration of the environmental factors that may influence the parental understanding of the trial.

Access to information
After reading the ICF and watching the video, majority of the parents suggested to have access to comprehensive (n=11). Having as much information will help them to make an informed decision to whether to participate in the trial. However, three parents stated the informed consent form as well as the video is enough, as more information can become overwhelming.

R: You get so much documentation and pamphlets, and it's like an overwhelming time in your life. You don't want more junk in your house. So, getting the consent form, the video and speaking to the researcher in the hospital is sufficient and easy to understand
Participant #2

Enabling resources
After reading the ICF, majority of the parents (n=11) stated that although lengthy it provided all the necessary information to make an informed decision. Some interviewees (n = 3) indicated that the ICF document is not an ideal source of information, as some stated it was overwhelming and contained medical jargon.

R: There's some medical jargon and it was hard to understand some aspects of the trial
Participant #9

One parent even mentioned the ICF being more of a legal document and preferred the video

> R: The consent form is exaggerating a bit to be on the cautious side. I felt like video, it is a little bit different than the consent form. The consent form is more like a legal document and the video is more informational.
> *Participant #1*

Eight parents thought the video was a great informational tool to help summarize the ICF and provide visual description of the trial.

> R: I'm a visual person, so I found the visuals quite helpful and less intimidating, I think as well, I could tell that the information was not to say less complex, but it was accessible. Even if English wasn't my first language, I still would be able to identify and understand everything
> *Participant #10*

Beliefs about Consequences

***N* = 13**

Although interview participants were hopeful regarding the potential of the stem cells, many indicated they were concerned about negative consequences like the risks and safety profiles as well as the unexpected outcomes.

Participants were most concerned about the potential safety and side effects associated with participating in a stem cell clinical trial and indicated that perceived risk played a part in their decision to participate. Nine participants mentioned the risk for negative side effects, two mentioned the risks of the treatment in comparison to the standard of care options and five mentioned uncertainty of Phase 1 trials. The ability to provide data on the efficacy may impact whether they will decide to participate.

> R: I don't want my child to be a guinea pig. Obviously, it would to be to benefit babies in the future and but am I willing to risk my child's life in order to see if there is a benefit.
> *Participant #5*

> R1: I can weigh the risks of administering the stem cells to the child compared to the risks of not administering them to him or her and staying on the ventilator for a quite a bit that may lead to chronic pulmonary problem
> *Participant #A02*

> R2: The other study that we are participating in, has 1000's of participants. This Phase 1 only had 9 and I don't want my child to be the first to receive the cells
> *Participant #5*

However few parents (n=4) mentioned that after watching the video the risks did not concern them, and that it was clear that the study team will monitor the baby regularly

> R: There's always risk. You know those side effects are things that there are options for. Should my child experience like you know, issues with blood pressure and things like that. There are things that you can do to address that
> *Participant #A04*

<u>Unexpected and expected outcomes</u>

After watching the video, few participants (n=4) mention that what will happen if the child has BPD and do all children on oxygen support will get BPD.

> R: The video could kind of scare some parents, right? Because my baby is on ventilation. Is this going to happen to my baby? So, like maybe making it clear like you said that this is an extreme case, so something like that because that was not clear in the video
> *Participant #3*

Majority (n=8) did mention having clear indication of the outcomes with or without receiving the cells is necessary. Providing information of other trials using this treatment may help aid in their decision making.

> R: Information on risk involved or like worst case scenario, nothing will happen. You know. Best case scenario we might see slight improvement, or this is these are the markers that we are looking for during the trial kind of thing to put me at ease. So, outcomes from the study
> *Participant #10*

Treatment Benefits

Participants were supportive of research that aims to improve current treatment options and contributes to developing a cure. Participants indicated that key benefits would include benefiting the child (n=7) as well as future children and parents (n=8).

> R: You know it's better to prevent than you know. Like she gets older, and then you realize that you should have done that. So, you take the chance to provide for a better life
> *Participant #12*

> R1: Like anything that could potentially benefit children in the future, so their parents don't have to, you know, go through as much as any other NICU equipment
> *Participant #3*

Long-term Benefits

One of the most cited benefits was contributing to science (n=7) and bettering our healthcare.

> R: I want to participate in any study I could. That's how we improve things. Yeah, that's how we discover new things. We discovered better ways to do that to heal people and etc. And the progress we've seen from the 70s up to now.
> *Participant #1*

One participant noted that advancing science may lead to decrease of public money for ICU costs.

> R: And when you think about the grand scheme of things, it's also you know public money that's being spent to help something that could be preventable. Everybody wins
> *Participant #M03*

Beliefs about Capabilities

***N*= 11**

Five participants indicated they would feel confident participating in a stem cell trial after reading the ICF. The main reason cited was the satisfaction of the information presented in the ICF.

> R: No, I think the consent form pretty much covered all bases.
> *Participant #4*

Five indicated they felt a lot more confident after watching the video to make an informed decision. Main reason was the visual description of the treatment (n=4) as well as understanding the reducing of risks of BPD (n=1).

> R: More confident than when we just read the paper. When we read just the paperwork, I think we're both kind of like pass
> *Participant #A05*

Although after reading the ICF and watching the video, four parents mentioned feeling somewhat confident because they are making the decision on their child's behalf (n=1), and they still would like to speak to a healthcare provider about the study (n=3).

> R: So, when it comes to my baby, I'm a little more hesitant, more hesitant than I would be for myself
> *Participant #A04*

> R1: having more conversations with the study team and care providers will help
> *Participant #10*

Goals

***N* = 11**

Quality of Life

Five participants were especially vocal regarding the importance of quality of life for their infant. One participant indicated that he would not want to regret participating in a study if the child developed BPD in the future.

> R: You want to prevent any negative effects, so you would want to give your child any treatment out there like whatever to help benefit them
> *Participant #11*

Benefits to Others

Though many interview participants recognized that although with a Phase 1 study there may not be a direct benefit, the main motivating factor was to advance neonatal care for other babies to benefit from (n=8).

> R: Our goal is to improve medicine and the more kids that participate the more advance neonatal medicine will be and increasing the survival rates and the gestation they are born at
> *Participant #1*

Intention

***N* = 13**

Five participants indicated they would participate in the trial after reading the ICF. After watching the video, 10 indicated that they would participate as it was more informative in comparison to the ICF.

> R: I think so, like given if it was something like this proposed study, I probably would
> *Participant #2*

> R1: If I was presented with video alone, I'd be more like very likely to say yes if I'm presented with the consent form alone, I'm most likely I would say no
> *Participant #1*

Two participants indicated they will not participate in the trial after reading the ICF because of the wording of the form. Additionally, two other parents indicated they will not participate in the trial after viewing the video because of their baby's health is a priority and would not take any chances.

> R: Unless the wording of the consent form changed because not 100% accurate. Like their exaggerating a bit to be on the cautious side, I would not participate.
> *Participant #1*

> R1: Knowing what we know I would say no cause there is no benefits and more risks. We already have pregnancies that didn't work so I wouldn't take the chance
> *Participant #12*

Few participants (n=4) wavered in their intentions and suggested they would participate if they had no other treatment option, whereas three participants said that they would reconsider the trial if there a direct benefit.

> R: Maybe if it was a life of death situation maybe I'll reconsider
> *Participant #5*

> R1: If it's solely just to test the safety of this procedure. I would say no to the trial. I am not sure what would really happen to my child
> *Participant #A03*

While motivation to participate was variable, this is likely to do with the participants that were sampled. Many of the people we interviewed were either had very sick babies or some had babies that were doing relatively well. Some parents had experienced previous loses in the NICU which could played a factor in their decision making. Most parents, however, did indicate participating in the trial after viewing the video to help improve their child's health.

Social Influence

***N* = 13**

Video influence

Participants identified four distinct influential entities in the video that would influence their decision making- The main PI narrating the video, incorporation of the ethics bodies, the case study, and the prompt at the end of the video to ask questions.

Principle Investigator

Participants (n=7) indicated having Dr. Bernard Thébaud in the video and having him narrate the video does influence their decision making. Many voiced out that it shows accountability as well as putting a face to the trial. However, few (n=3) did mention that they would like to speak to him in person rather seeing him on video, because the video is general and not relatable to their baby's health.

> R: Having him in the video you can see and hear like the actual person doing the study talking about it, that helps.
> *Participant #4*

> R1: Dr. Thébaud narrating the video does not really change a lot for me. Whether it's him or somebody else, unless I can talk to him face to face and that's where I'm going to actually be more comforted if I come face to face because I know because the video is general
> *Participant #1*

Depiction of the regulatory bodies

Many parents appreciated us including information about the regulatory bodies (n=8). Many stated it helps understand the regulatory component as well as they will be monitoring the study continuously. This provides comfort and aids in their decision making.

> R: Knowing that there's an Ethics Committee and the extensive vetting that goes through this, at least here in Canada before things get put into place. Knowing that really helps
> *Participant #10*

Prompting questions

At the end of the video we encouraged the viewers to ask questions. This was appreciated by parents (n=5), some even stating that it opened up a conversation and also asking questions they would have never thought of if not for watching the video.

> R: I think from the video is to kind of Like prompt questions if there right instead of like confusing, and so like I think it was like a good opportunity for a discussion point without it getting too complex.
> *Participant #A03*

Case study

Finally, many parents appreciated the inclusion of a case study of baby Olivia with BPD. Many stated that it helps with relatability and how extreme BPD can cause complications (n=6). Few did mention, however, that it might make parents believe all babies with BPD will end up like Olivia (n=2). Nevertheless, having Olivia's story included resonated with parents and made them think of the actual consequences of BPD.

> R: I think initially, hearing or seeing Olivia's story was helpful in terms of relatability. You know, hearing a story. Very similar circumstances really of extreme prematurity.
> *Participant #10*

> R1: Well BPD is on a spectrum and parents may thing that by seeing this case they would copy and paste. It might give off a false sense awareness
> *Participant #A04*

Neonatologists and bedside nurses

Few parents (n=6) mentioned that they would be influenced by their attending neonatologists' opinions since they know their baby best as well as they are confident and knowledgeable about the disease.

> R: For me I would reach out my baby's doctor. If they feel alright, I would be more inclined to participant
> *Participant #4*

Not only the neonatologists' opinions matter but also the bedside nurses (n=6). Parents were more inclined to seek advice from the nurses since they seem them more frequently and a lot more personable

> R: Practically speaking, like day-to-day, we see our nurses 100% more often than doctors, so I'm like you might get a couple of check-ins per week with a doctor, but the nurses would probably be more important if they felt comfortable explaining things like this.
> *Participant #2*

Friends and Family

Surprisingly, friends and family were not an important source of advice and counsel. Majority have said that they would discuss this trial with their partner rather than other family members, since they would know best for their child (n=7).

> R: I said I would need to talk to my wife first, but it would be a very long conversation, but I would
> *Participant #A03*

> R1: I wouldn't talk to my family members about it. There are so many other things going on with preemies that like why would you? You have to kind of concentrate on like the main things, updating your family members so this wouldn't be like a main thing
> *Participant #2*

One participant did mention of bringing this trial to the attention of other family members since they are all very close and it is great to get a second opinion.

> R: I would discuss this with my mother in-law. In the other study we asked for her opinion
> *Participant #A03*

Two parents did mention having doctors in their families. They indicated that hearing from their friends with medical backgrounds would be important to them and would provide non-bias answers.
While there are some exceptions, neonatologists, and bedside nurses where the most trusted influence for parents.

Research Staff

When asked who they would like to hear the study from, five participants mentioned that hearing the trial from the research staff is suffice as they can provide important study details (n=5). However, they mentioned that having the PI available to answer questions will help with their decision making.

> R: I think it's fine with one of the research assistants providing information but making the neonatologists available for any additional questions if necessary
> *Participant #3*

Chapter 3- What are the potential barriers and enablers to research personnel participation in a Canadian cell therapy trial in neonates? A stakeholder interviews

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Intended Journal: Trials

Abstract

Objective: Early phase cell therapy trials face many barriers to successful timely completion of the trial. To optimise the conduct of a planned clinical trial of mesenchymal stromal cell (MSC) therapy for bronchopulmonary dysplasia, we sought research personnel views on possible barriers and enablers that may influence their recruitment in a MSC trial.

Study design: We conducted interviews with research personnel from Canadian level 3 Neonatal Intensive Care Unit (NICU) sites. We used direct content analysis to identify relevant domains reflecting the key factors that may affect screening and recruitment. Interview guides and directed content analysis were framed using the theoretical domain framework (TDF) to identify factors that may impede or enable research personnel to recruit for an early phase regenerative medicine trial.

Results: In total we interviewed 14 research personnel. Research personnel expressed "cautious hope"; while motived to approach patients for the trial, many expressed safety concerns. Regardless, (n=14) all intended to recruit for this trial (domain: Beliefs about Consequences, Goal, Beliefs about Capabilities, Knowledge, Intention). Research personnel mentioned "coordinating between people" including having support from clinical staff for participant recruitment can be a barrier to trial recruitment (domain: Social Influence). Although, speaking to parents is part of their role, they mentioned due to the "challenging context" of the study, they prefer to have clinicians involved with the recruitment and speak to parents about the trial. Having resources available to educate the research personnel but also to help parents understand (including the use of the animated video) will improve recruitment (domain: Beliefs about Capabilities, Environmental Context and Resources). "Optimizing study flow", was a common concern for research personnel; time sensitivity of recruitment period and other competing studies may lead to missed participants (domain: Nature of Behaviour, Behavioural Regulation and Goals).

Conclusion: Research personnel play a key role in recruiting to early phase trials in the NICU but factors affecting their recruitment activities are under-studied. Integrating this stakeholder group into planning recruitment for a clinical trial of mesenchymal stromal cells in neonates can help with trial optimization. The methodological approach taken herein could be extended to understand coordinator barriers/enablers for other early phase clinical trials in pediatrics.

Introduction

Every year, an estimated 15 million babies are born preterm [1]. Preterm birth complications are the leading cause of morbidity and mortality in infants worldwide [1]. One of the most prevalent lung complications seen in extreme premature babies is bronchopulmonary dysplasia (BPD) [2]. Unfortunately, there is currently no cure for BPD and many babies face life-long respiratory and neurological impairments [3]. Recent preclinical data supports the use of mesenchymal stromal cells (MSCs) as an effective treatment for BPD, given their potential regenerative, anti-inflammatory, and immunomodulatory properties [4].

Clinical trial feasibility depends on several factors; one of particular importance is recruitment rate[5]. Trials often experience delays due to recruitment of eligible participants as much as 86% of trials do not meet recruitment numbers by the deadline and 19% are terminated early [6]. There is an increased importance of involving key stakeholders when developing clinical trials to anticipate and address issues that may affect the feasibility and recruitment to the trial[7–9]. Given the complex, resource-intensive and the nature of MSCs, recruitment strategies must be optimized to achieve the intended sample size. A recent study explored patient and physician-related barriers and enablers to participating in a MSC clinical trial for the treatment of BPD[10]. Barriers included side effects, unexpected outcomes, and lack of knowledge of clinical trials. Key enablers included altruistic benefits, and having informative conversations with clinical personnel[9,10]. Common reasons for parents declining their child's participation in clinical trials include inconvenience to the parents, risks associated with the investigational treatment, burden to the child's health and the limited time available to make an informed decision[11].

Physicians can encourage trial participation by addressing patient concerns and explaining trial risks and procedures[12]. However, due to lack of time and other pressing commitments, physicians are not readily available to speak to patients[9]. Research personnel (recruiters: research assistants and research coordinators) play an important role in the recruitment process, as they actively screen and interact with potential participants for clinical trials[13]. Despite their influence on recruitment, most research has been focused on barriers to clinical trial recruitment relative to medical professionals and patients[13–15]. Research drawing upon participants' perspectives and experiences is increasingly being undertaken as part of clinical trials to help inform recruitment, trial delivery and improve the conduct of future trials. Exploring research personnel perspectives can be used to improve recruitment, adherence to trial protocols and the support given to individuals working on future trials. The information gathered will help to further optimize trial feasibility and enhance recruitment procedures[16].

Low recruitment and retention rates increase the cost of research, leads to research waste, lowers the validity of studies, slows innovation, and prevents timely implementation of effective care[5,6]. Work has been done to optimize trial recruitment by drawing on theory[7–10]. For instance, to address parental concerns, our study team developed an animated informational video to be used as a consenting tool[10]. Consent forms can be intimidating to read, especially if your child is in critical care[17]. By incorporating a multimedia tool, we aim to increase comprehension, satisfaction, and decrease anxiety[18,19]. Adding this tool to the standard consent process can contribute to reducing misunderstanding and avoid 'non-informed' consent[13]. This tool can help give all the essential information to parents when considering trial participation. Prior to early phase MSC trial

launch, it is imperative to analyze if this tool will be used by the research personnel when recruiting participants. To conduct a robust trial, it is essential to identify barriers from the staff that hinder screening and consenting in patients for an interventional stem cell therapy trial.

Understanding factors affecting research personnel recruitment activities could be aided by drawing upon frameworks that list common barriers and enablers. For instance, the Theoretical Domains Framework (TDF) synthesizes theories of behaviour change into set of domains that represent influences on decisions and actions[20,21]. A few reasons why researchers use this framework include the direct link to theory on factors known to affect decision-making and behaviour shown in Table 1[20,22]. Using a comprehensive, qualitative interview approach, we applied the TDF to investigate barriers and enablers that would influence research personnel screening and recruitment in a clinical trial of MSC therapy to treating BPD. Despite the emerging body of evidence of regenerative medicine therapies, the existing literate lacks the discussion of these therapies in neonates. Thus, strategies are required to translate these therapies into the neonatal intensive care unit (NICU). The present study aims to explore the views of NICU research personnel to understand the barriers and enablers to early phase stem cell therapy trial recruitment.

Table 1. Theoretical Domain Framework (Version 1 and 2) domains and associated definitions

Domain (TDF-V1)	Domain (TDF-V2)	Definition [21]
Knowledge		Existing procedural knowledge, knowledge about guidelines, knowledge about evidence and how that influences what the participants do
Skill		Competence and ability about the procedural techniques required to perform the behaviour
Social/professional role and identity		Is the behaviour something the participant is supposed to do or someone else's? (When discussing 'we'/the collective) Boundaries between professional groups
Beliefs about capabilities	**Beliefs about capabilities**	Perceptions about competence and confidence in doing the behaviour
	Optimism	The confidence that things will happen for the best or desired goals will be attained
Beliefs about consequences	**Beliefs about consequences**	Perceptions about outcomes and advantages and disadvantages of performing the behaviour or pervious experiences that have influenced whether the behaviour is performed or not
	Reinforcement	Increasing the probability of a response by arranging a dependent relationship, or contingency, between the response and a given stimuli
Motivation & Goals	**Intention**	Conscious decision to perform a behaviour or a resolve to act in a certain way
	Goals	Priorities, importance, commitment to a certain course of actions or behaviours intentions
Memory, attention, and decision making		Attention control, decision-making, memory, i.e. is the target behaviour problematic because people simply forget?
Environment context and resources		How factors related to the setting in which the behaviour is performed (e.g. people, organisational, cultural, political, physical and financial factors) influence the behaviour
Social influences		External influence from other people, views of other professions, patients and families, doing what you are told and how that influences what you do
Emotion		How feelings, affect (positive or negative) may influence behaviour
Behaviour regulation		Anything aimed at managing or changing objectively observed measured actions
Nature of Behaviour		Relates to the history of the behaviour, and one's experience with said behaviour

Methods

The study was approved by the Ottawa Health Science Network Research Ethics Board and CHEO (20200545-01K). Verbal informed consent was obtained from all participants, and all procedures followed were in accordance with institutional guidelines.

The consolidated criteria for reporting qualitative research (COREQ) reporting guideline was used for this study[28]. The checklist guided the research methods, findings, analysis, and interpretations[28]. We used the validated version of the TDF to frame the interview guide and kept the domain that was removed from the validated version (nature of the behavior) because it

captures unique information helpful in understanding participant experiences with screening behaviors[21]. The 15 domains used in this study are presented in Table 1. The guide was developed in collaboration with a health psychologist (JP) and a NICU research coordinator (CH). The behaviour of interest was defined using the Action, Actor, Context, Target, Time (AACTT) framework (Table 2) [20,21]. See Appendix A for the detailed of the interview guide.

Table 2. Action, Actor, Context, Target, Time [20,21]

AACTT	Clinical research personnel behaviour
Action	Consenting/ providing all the informational needs to parents for a planned multi-center MSC trial for BPD
Actor	Level 3 Canadian NICU Research Coordinators
Context	Neonatal Intensive Care Unit
Target	Parents of extreme preterm infants, at the highest risk of developing severe BPD
Time	After 7 days of life ventilated

Snowball sampling was used to identify 14 level 3 NICU clinical research personnel across Canada. Potential participants were approached with an information sheet sent by email. We asked each participating researchers to identify additional research staff working in their center for interviews who may offer differing views.

A master's student (KS) with background in health science was trained in conducting interviews and using the TDF to inform data collection and analysis. The research assistant conducted all interviews by Zoom. Sample size was determined using a 10+3 stopping rule[23]. Data was considered adequate (thematic saturation) if no new themes emerged within the last three consecutive interviews.

Semi-structured interview guides were used, and during the interviews, participants were encouraged to expand on their answers. At the beginning of the interview, the master's student (KS) explained to the clinical research personnel about the research activities for the upcoming multicenter MSC trial to treat BPD, including the recruitment window for the trial being 7 to 21 days of life. KS explained the main goal is to understand their recruitment process and if they can provide all the informational needs to potential participates to consent to a cell therapy trial. During the interview, she described the mechanism of action and showed them an animated informational video about the trial, which was produced by collaborating with neonatal families, as well as CHEO's Parental Advisory Committee. This tool may be used to help with recruitment of eligible patients into the study. All interviews were recorded, transcribed, and anonymized.

Data analysis

Using NVivo 12 (qualitative software), a directed content analysis was conducted[24]. The interviews were transcribed and verified by interviewer (KS) prior to analysis. The analysis involved the following steps consistent with standard recommendations for TDF-based qualitative studies:[20–22] (1) coding, which represents linking participants' responses to theoretical domain using a codebook, (2) generation of specific belief statements a collection of responses with a similar underlying belief that suggest a problem and/ or influence of the beliefs on the target

behaviour[22],and (3) identification of key theoretical domains[25]. Overarching key themes spanning the relevant domains were then generated.

Code book development and coding to TDF domains

The first two interviews were independently double-coded, and the two coders compared their coding to develop a coding book. The code book was developed to maintain coding rule transparency and help code the rest of the remaining interviews. Analysis was led by a primary analyst (KS) who coded each interview and allocating relevant experts into one of the theoretical domains from the validated TDF version[21,22,26]. A secondary analyst (GC), blinded to the primary researcher's coding, subsequently coded the excerpts to the TDF domains. Conflicts were resolved through discussion. The code book was used to code the next two interviews independently. Assessment of inter-rate agreement using Kohen's Kappa was conducted for the second two interviews; a priori it was planned that if kappa inter-rater agreement scores did not reach threshold (0.80), single coding would not occur for the remainder of the interviews[27].

Coded data excerpts were converted into belief statements by KS and revised by a health phycologist (JP). To document the progression from data excerpt to subtheme, we created belief statement tables showcasing subthemes, belief statements, exemplary quotes, frequency counts (number of participants endorsing a belief). We identified key domains according to frequency of beliefs, presence of conflicting beliefs, and relevance of recruiting behaviour [22].

Results

Participants

Interviews were conducted between October to December 2020 and lasted between 24 and 60 minutes (median, 35 minutes). Fourteen research personnel (two men) and (twelve female), from twelve level 3 NICU centers across Canada participated in the interviews. Research personnel reported having experience recruiting patients for research studies for 1-15 years. Participant's characteristics are described in Table 3.

A total of nineteen research personnel from fourteen level 3 Research NICU centers were approached and fourteen research personnel from twelve sites agreed to participate (spanning Canadian provinces British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Quebec, and Nova Scotia). Five participants declined to participate due to scheduling issues.

Table 3. Sample characteristics for research coordinators (n=14)

Characteristic	n (%)
Gender	
Male	2 (14)
Female	12 (86)
Experience as a research personnel	
0-5	7 (50)
>5-10	4 (29)
10+	3 (21)
Location of NICU research personnel	
British Columbia	1 (7)
Alberta	4 (29)
Saskatchewan	1 (7)
Manitoba	1 (7)
Ontario	5 (36)
Quebec	1 (7)
Nova Scotia	1 (7)

Inter-rater reliability

Data from research personnel were analyzed together and consisted of 67 belief statements across 13 domains (Appendix B). The first four transcripts were double coded by two researchers; kappa inter-rater agreement score for the four interviews was 0.95, indicating agreement and that interviews could be reliably coded into respective domains[27]. The remaining transcripts were then single-coded (KS).

Relevant domains

Analysis of barriers and enablers deemed relevant in nine for our target behavior: Goals, Social Influence, Knowledge, Intention, Beliefs about Consequence, Beliefs about Capabilities, Behavioral regulation, Nature of Behaviour, Environmental Context and Resources. A comprehensive list of detailed belief statements and subthemes associated with each domain are shown in Table 4. In depth analysis of the belief statements can be found in Appendix C.

Table 4. Summary of belief statements and sample quotes from participants assigned to domains identified as relevant

Relevant Domain	Subtheme	Sample belief statement	Sample quotes
Key theme 1: Cautious Hope			
Knowledge	Knowledge of therapeutic treatment	I am aware of mesenchymal stromal cells (7)	"BPD is familiar to me as well as mesenchymal stromal cells"-Participant 9
		I have little to no knowledge of mesenchymal stromal cells (7)	"I have heard of it but do not have ton of knowledge"- Participant 2
Beliefs about consequences	Expected and unexpected outcomes	Unknown safety and efficacy (11)	"The one concern for me is pulmonary embolism. It isn't really something that we see in these babies, so that might be a bit concerning because that's something That's new to this population for the most part." – Participant 8
Beliefs about capabilities	Confident	I feel confident in my ability to screen/ recruit patients for this study (11)	"I would still feel comfortable. I think because I could speak to the earlier phase to give some confidence and some credibility to the study and to give rationale that we're continuing to build on the knowledge we've already have" -Participant 11
		I am not confident in my ability to enrol for a Phase 1 trial (1)	"Honestly, it makes me feel a little bit hesitant just because it is such a new therapy. And like you said it's Phase 1, so it's really early on so it makes me a little hesitant in the fact that I don't know the adverse outcomes."-Participant 5
Goal	Advancing science	Approaching patients is important to contribute to this field (12)	"Advancing respiratory care is a huge thing. BPD is at an absolutely high rate in Canada and wanting to reduce that would be amazing for the overall benefit of future babies and the baby that we're treating."- Participant 12
Intention	Intent to participate	I intend on approaching parents for this trial (14)	"I think if the phase one was done and we had information that showed success or if you reached your primary outcome, which is the safety, feasibility and so forth. I will definitely approach parents"- Participant 4
Key theme 2: Coordinating between people			
Social Influence	Support from colleagues	Opinions of other colleagues' matter before approaching patients (8)	"One of the neonatologists was not keen on us approaching parents for whatever reason, whether we thought it was valid or not. I just abandoned it. If they were aware about why this study was being done, the outcome may have been different." -Participant 8
Key theme 3: Challenging Context			
Beliefs about capabilities	Confidence to approach parents	Neonatologists should be involved with the consenting process (11)	"Some form of neonatologist might be helpful to be involved, or like a fellow doctor for answering questions. The physician caring to the baby should be involved."– Participant 2
	Confident to screen with video	I feel confident in my ability to screen/ recruit patients for this study with the use of the video (12)	"Having the video is great. Everyone have phones. so, I think that's feasible. And it is not very long, it is a short video."-Participant 7
	Consenting resources	Other consenting resources (13)	"Having like these recaps of a study. What it looks like. And they just put all the results of the study. But

Environmental context and resources			doing that in the consent format such as a this is a problem, these are the opportunities, this is what is known, and this is the study like in a one in drawing and pictographs" -Participant 5
		There is no need for other consenting resources (1)	"I honestly find that the more information I give to parents, the less they consent."- Participant 6
Key theme 4: Optimizing study flow			
Nature of behaviour	Current and past recruitment experience	I have a plan when I recruit parents (3)	"The more difficult studies are the ones to recruit on day zero. I think you know, with the stress of delivering premature baby and then having to talk to parents about a study during that time I think plays a part in a lot of them refusing consent… I usually know where the mom is, and we meet in her room or make an appointment to meet. I usually try to get consent at the bedside." – Participant 13
	Recruitment target	I achieve my recruitment target (7)	"We do pretty well. We get a reasonable number of yeses compared to nos. I think we've perfected our consenting process pretty good. We do a good job at informing our patients" -Participant 9
Behavioural regulations	Coping plans	Alternative plans when approaching parents with multiple trials (5)	"Part of their mandate is to discuss competing studies and how those will be managed. So, studies are prioritized based on the therapeutic benefit and the risk profile." -Participant 10
Goals	Priorities	I have other competing priorities (7)	"We have to prioritize studies on the unit where those that have the greatest therapeutic benefit for patients. "- Participant 10

[a] Numbers in brackets indicate how many participants endorsed a specific belief statement

Key theme 1: Cautious Hope (domain: Beliefs about Consequences, Goal, Beliefs about Capabilities, Knowledge, Intention)

Research personnel perception of the planned umbilical cord-derived MSC therapy trial at multiple centres were cautiously hopeful with recruitment. Most research personnel (n=12) felt optimistic about the MSC trial and were motivated to routinely screen and approach eligible participants for the trial. The main motivating factor for recruiting is to decrease the incidence of BPD (domain: Goals). Regardless of the concerns, all research personnel intended to facilitate recruitment for this trial (domain: Intention)

> "I think if the phase one was done and we had information that showed success or if you reached your primary outcome, which is the safety, feasibility and so forth. I will definitely approach parents"- Participant 4

Specific knowledge of MSCs varied across participants; some expressing having knowledge of stem cell research (n=7) while others had very limited knowledge of the treatment (n=7) (domain: Knowledge). Many voiced out, since this is an early phase trial, safety of the MSCs would be a concern while recruiting eligible participants and desired to know more about the Phase 1 results, including response rates, and toxicity (n=11) (Domain: Beliefs about Consequences). One research personnel mentioned having full transparency with participants will help further facilitate conversation.

> "You know, many of them being new parents and maybe first time in the hospital. Those things can be scary, so I think it's important in the consent forms to really demonstrate what is the likelihood of the risk right? That helps inform the conversation and makes a huge difference"-Participant 8

One research personnel reported feeling discouraged or demotivated to recruit more participants if the participants in this study showed any side effects (domain: Beliefs about Capabilities). While others (*n*=11) felt confident to approach participants about this early phase MSC trial, regardless of the trial outcomes, most believed MSC therapy would benefit their participants and fill significant treatment gaps (domain: Belief about Capabilities).

> "I would still feel comfortable. I think because I could speak to the earlier phase to give some confidence and some credibility to the study and to give rationale that we're continuing to build on the knowledge we've already" -Participant 11

Key theme 2: Coordinating between people (domain: Social Influence)

Most research personnel (n=8) touched on the topic of influence from other colleagues (clinical staff), who are not directly related to the trial, as having a potential negative impact on recruitment (domain: Social Influence). Many discussed that having a demanding clinical workload, high turnover, and uninterested staff are reasons for lack of engagement. Prior to being introduced to the participating families, research personnel need to speak with the clinical staff to ensure the parents are eligible for the study. Engaging with and motivating clinical staff can help encourage parents to participate (domain: Social influence).

> "What's key is that we educate nurses during their mandatory education days right now. Families have struggled when they've consented to a study, and then the nurses aren't aware of what's going on. Basically, educating the bedside nurses and what's going on can really, really add to the success of consenting and the success of this study"- Participant 14

Key theme 3: Challenging Context (domain: Beliefs about Capabilities, Environmental Context and Resources)

Research personnel preferred to have the attending physician involved when recruiting (n=11) (domain: Beliefs about Capabilities). Many felt that having a physician alongside with them will help answer more of the heavy knowledge-based questions that they may not be qualified to answer (Domain: Beliefs about Capabilities). Seeking help from higher qualified colleagues can assist with achieving higher recruitment numbers.

> "Having the neonatologist involved might be helpful, or like a fellow doctor for answering questions. The physician caring to the baby should be involved. The families are very interested in how this will affect the overall care of the baby, right?"- Participant 12

Nearly all research personnel (n=13) indicated that additional resources are required to provide all the procedural information to parents. One research personnel noted the consent form can

overwhelm parents and make them feel even more confused (domain: Environmental Context and Resources).

> "Pamphlet might be nice. The consent form is not as approachable, that they may not be able to communicate back. Something like a lay pamphlet to really discuss what it is, what the benefits are, what the risks are just a very kind of quick summary that's more approachable, then the long, six, seven-page consensus to give would be good."- Participant 2

The research personnel were shown the animated video during the interview, and all expressed that the animated video is a great way to show risks of the treatment and give parents an overview of the study. Almost all (n=12) research personnel stated that the use of the animated video tool made them feel more confident to approach families for this trial (Domain: Beliefs about Capabilities).

> "I think the video will bring everyone to the same mental model instead of them, sort of figuring it out in their head. So video is very helpful, and I would use it for sure… For families, or for anyone who sees that video to realize it's more than one person, yeah, and that there is a team approach, but that is that is shown enough."- Participant 4

Key them 4: Optimizing study flow (Domain: Nature of Behaviour, Behavioural Regulation and Goals)

Some research personnel mentioned time pressure (n=3) (recruiting babies at day of life 1) during recruitment and suggest having a clear plan of action before delivery may improve recruitment (domain: Behaviour regulation). However, when mentioned that the recruitment window is between 7 to 21 days of life, research personnel expressed being content with the timelines.

> "The more difficult studies are the ones to recruit on day zero. I think you know, with the stress of delivering premature baby and then having to talk to parents about a study during that time I think plays a part in a lot of them refusing consent… I usually know where the mom is, and we meet in her room or make an appointment to meet. I usually try to get consent at the bedside."- Participant #13

Many research personnel (n=7) said they usually achieve their recruitment goals regardless of the Phase of the study (domain: Nature of Behaviour).

The topic of multiple competing studies was also mentioned. Seven research personnel indicated that other studies within their unit may take precedence over this study (domain: Goals). Most research personnel have coping plans when multiple studies are active. Five research personnel expressed strategies including prioritizing studies that have the most benefits, advising families that they will be approached for multiple studies throughout their NICU stay and take one study per population (domain: Behavioral Regulation).

> "Our plan is to do only one study per kind of population. Like if we chose to do your trial, we would make sure that there's nothing else that's overlapping."- Participant 9

One research personnel mentioned eliciting help from colleagues when other active studies are present (domain: Behavioral Regulation).

> "Part of our mandate is to discuss competing studies will our committee and how those will be managed. So, studies are prioritized based on the therapeutic benefit and the risk profile." -Participant 10

Discussion

Previous efforts to improve trial recruitment have rarely used theory-based approaches, especially for resource-intensive trials. With translation of potential life-saving therapies being slow and only a few high-impact preclinical therapies successfully translated into clinical practice, it is important to identify strategies to optimize trial execution[29]. This is the first study to explore, through an ethical lens, the usage of the TDF, to improve recruitment for early phase clinical trials in the NICU. After analysing the interviews, it was evident that the NICU research personnel were highly motivated to recruit for an umbilical cord derived MSC trial and wished to know more about the efficacy and toxicity of the treatment. Many indicated having all details of the therapy would help facilitate conversations with parents. Research personnel also identified several barriers including coordinating recruitment with other clinical staff, recruiting for multiple active studies, the need for improved education about the trial for staff. The research personnel also suggested having the physicians available for clinical questions when speaking to parents. Supporting a research culture, having available resources and imporved focus of research, were all aspects found in other studies on trial recruitment [5,30–33]. Our study highlights and adds to this knowledge base of barriers and enablers to trial recruitment in the NICU.

One potential barrier that could hinder recruitment to the trial is other competing trials. It is not uncommon for multiple clinical trials at the same institution to recruit concurrently from the same patient population. Many research personnel indicated that they present all active studies to parents in the unit. Although parents like the option to pick and choose which study to participate in, parents may feel overwhelmed and hesitant due to multiple trials, hindering their urge to participate in this study[34–36]. Research personnel mentioned the recruitment window for this early phase trial is ideal, as parents have ample amount of time to make an informed decision. Sites can also establish which studies have priority by analyzing patient criteria, the disease of interest, available funding, and institutional self-interest[37]. If the institution is transparent with the investigator about the prioritising criteria, the lead investigators can choose which sites will be the best fit to execute their trial[33]. By minimising the number of studies competing for the same participants, the prioritisation of clinical trials can also aim to reduce the number of eligible research participants exposed to risk associated with different studies [33]. These criteria will help minimize the loss of recruitment.

Research personnel did say that their recruitment interaction with parents was relatively successful. Although recruiting potential participants is part of the researchers' role, available

support from the attending neonatologist or a member of the clinical team would be beneficial. One study examined reasons for parental consent in a High-dose Erythropoietin for Asphyxia and Encephalopathy (HEAL) trial, and it was reported that 71% of parents had trust in the medical professionals prior to trial consent[38]. Other studies have similarly found the positive influence of clinicians on parental consent[36]. Research personnel mentioned, since this MSC study is relatively new to the field, having the clinical staff familiar with the trial would help answer any heavy knowledge-based questions that the parents might have. However, to respect physician workload and time, it will be beneficial for research personnel to adopt strategies (educational training, support documents) that give themselves the tools to educate parents.

The difficulties of explaining the risks and benefits of the MSC treatment was another barrier research personnel mentioned. A systematic review of interventions to improve recruitment found researchers had communication challenges due to participant difficulty understanding trial concepts[5]. We suggest training programs, including the discussion of comparative data on treatment efficacy, compare toxicity of similar MSC therapies and to compare to standard of care treatments[8]. Having few, but detailed learning programs can improve the recruitment rate. A study has shown that training, which lasted only 4 hours, reported a recruitment rate increase of 15%, from 43 to 58 %, in participants[39]. Well-informed research personnel with informational resources will facilitate stronger researcher-participant discussion. The research personnel also appreciated the animated video, as it is a useful resource to be used in their consenting process. The advantage of having this multi-media tool to address pertinent study details promotes stronger discussion with parents[40]. The research personnel can use the teach-back technique during the consent process, ensuring the parents understand trial details prior to consent[40].

Moreover, we learned through interviews, that building a research community by collaborating with the clinical professionals, is very important to the success of the trial[31]. Research personnel mentioned the positive impact clinicians and bedside nurses have on families' decision-making process[30]. It is the research personnel's role to engage with the clinical staff, persuade them of the relevance of the trial and to encourage prioritization implementation of new therapies in health care[5,30,32,41]. By educating the clinical staff and showing the potential benefits of the MSC treatment, we can exponentially improve trial recruitment. Lewingting *et al*., mentioned the importance of feedback on research results to the clinical team, as this keeps everyone informed[31]. Presenting at grand rounds, educational sessions (lunch and learns) and having one-on-one discussions are a few strategies we can incorporate[41]. Successful trial implementation is more likely to occur when the study team can build strong awareness and partner with important clinical members that have frequent interactions with parents of neonates.

Strengths and limitations

The strength of the study lies within the use of the TDF to identify factors that may impact research personnel recruitment behaviours. The TDF enabled a comprehensive assessment of the potential barriers and enablers to recruiting for an early-phase MSC trial. Findings when using qualitative methods to surface unanticipated barriers include the importance of educating research personnel, competition with relative NICU studies, and strong collaboration with clinical professionals. The TDF enabled linking research findings to theory to generate evidence-based strategies, which can be implemented by other trialists[42]. We also actively solicited knowledge and expertise from an important, under-studied stakeholder group that is key to trial recruitment.

Interviewing with this group about their thoughts on the MSC trial, in the development and execution process of the upcoming MSC trial can influence research prioritization for this future early phase MSC clinical trial. Also, engaging with personnel from potential research sites for our multi-center trial spreads awareness. The research personnel were eager and enthusiastic to join the study. This engagement is reassuring to our team as we seek to expand enrolment. Our study had some limitations; one being identified relative themes are based on research personnel's experience(s) and what they think the best practices are for recruitment efficacy. Further evaluation of these factors should be explored to assess the effectiveness. The other limitation is that we captured hypothetical barriers and enablers to participating prior to the multi-phase MSC trial. In the future, when the trial expands to other sites, there can be an assessment of the experienced barriers and enablers, and whether the trial recruitment activities sufficiently addressed anticipated barriers and enablers identified here. Nevertheless, findings from this study can be the basis for other investigators looking to use the TDF in a similar context.

Conclusion

This study is the first to bring a theoretical view to understand how to improve clinical trial recruitment with researchers in the NICU population. Our study focused on research personnel perspective to identify important barriers to recruitment of parents in an early phase clinical MSC trial. These results utilize the TDF to inform and enhance trial design for this early phase clinical trial by addressing challenges of recruiting for clinical trials. The TDF framework also provides a clear approach to understanding these factors when implementing strategies for effective recruitment. The profound trust parents have in researchers and the research system must be acknowledged. Our findings, although useful for this trial, can help other investigators in the near future.

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Appendix A: Interview Guide for Research Staff Members

Introduction:
Thanks for speaking with me today. I'm Kiran, a research assistant in the NICU working with Dr. Thébaud who is one of the neonatologists at The Ottawa Hospital. Our discussion will take approximately 30 minutes. Our discussion will be audio recorded to make sure that I capture all your thoughts. Don't worry; all identifying info (your name/names of others) mentioned will be removed and replaced with a code. If you want to take a break or stop or if you wish to withdraw from the study, you are completely free to do so at any point.

Dr Thébaud is planning an early-phase clinical trial to test a stem cell therapy using mesenchymal stromal cells (MSC) to treat BPD in very premature newborns. We want to make sure we consider the views of those who would approach/consent patients and communicate with parents when planning our trial so that we make sure the protocol aligns with your views and workflows in as much as is feasible rather than making assumptions. For example, we developed an informational video for parents to help support decisions about the trial and we'd love your views on it and the practicalities of using it with potential parents.

So, I have a set of questions about your views about this upcoming trial and the animated video and if this tool will help improve seeking consent of neonatal patients for our planned trial, and what your thoughts are about our video as it stands. Your answers will help to optimize our protocol to make it as workable as possible in any future trial.

There really are no right or wrong answers to the questions; I'm just interested in your honest opinions. Any questions?

Background

(Record whether male or female)

To begin, what is your current job title?

How long have you been in this job for?

In your center, do the research staff (coordinators, assistants, research nurses) screen patients for trials? (If answer is no: Do/could they contribute to identify potential patients for trials and liaise with the neonatologists?)

1. Can you tell me about your past experience consenting any patients for any clinical trial? (DOMAIN: NATURE OF THE BEHAVIOUR)
    - PROMPT: Have you consented patients for trials in the past?
    - PROMPT: (If yes) How did that go? Did you achieve your consent rate for your site?
    - PROMPT: Have you ever received training to consent patients for a clinical trial as a clinician? (DOMAIN: SKILLS)
    - PROMPT: If not, what sort of training would you need? What sort would you recommend to others?

2. What do you know about mesenchymal stromal cells (MSCs) in general, and for bronchopulmonary dysplasia (BPD) in particular? (DOMAIN: KNOWLEDGE)
    - Prompt: What information would you need to feel comfortable screening patients for participation in a trial of MSCs for BPD? (DOMAIN: KNOWLEDGE)

- PROMPT: Have any parents ever asked you about stem cell therapy? What was discussed? (DOMAIN: NATURE OF THE BEHAVIOUR)
- PROMPT: in your opinion, how much of a priority to you is MSC research in BPD?

Background info about MSCs:
- A type of stem cell.
- Stem cells well known for their ability to develop into variety of cell types and to renew themselves.
- Lots of research done on using these cells to treat and prevent diseases. Bone marrow transplantation of hematopoietic stem cells (the ones that give rise to all blood cells) used for treatment of some types of cancer for more than 40 years.
- MSCs another type of stem cells found in the bone marrow but can also be extracted from umbilical cord.
- MSCs show very promising results in the lab in treating various diseases.
- Main mechanism of action seems to be anti-inflammatory.
- Adult clinical trials with MSCs now running for several diseases: MS, Crohn's, stroke, and spinal cord injury.
- In neonatology, MSCs seem particularly promising in preventing and treating BPD. Evidence from animal models of BPD shows that MSCs are lung protective. A first human trial was published in 2014 showing feasibility and safety of intratracheal transplantation of MSCs in 9 preterm infants.

We are planning to run a first in Canada early phase trial of MSCs for BPD. But prior to conducting that trial, we want to make sure to build in your views about screening potential babies for an eventual trial of MSCs to preterm infants.

In relation to that and for the rest of our discussion, I would like you to think of the following specific activity:

You <u>personally screen/identify extreme preterm (born at less than 28 weeks GA)</u> at risk of BPD, for potential participation in a clinical trial of MSC therapy. For short, I will call this "approaching/ consenting potential patients" for the remainder of our discussion but by that I mean this more specific activity.

General first question:

3. Thinking about your own experiences, what might be some reasons that you would not be able to consent potential patients for a clinical trial? (DOMAIN: DEPENDS ON RESPONSE)

4. Imagine yourself identifying a potential patient. Can you briefly walk me through the steps that you would use to approach a potential patient for a clinical trial? (DOMAIN: KNOWLEDGE)

5. What are the specific techniques or skills that you need to approach/ discuss potential patients for enrollment for this trial? (DOMAIN: SKILLS)

6. How do you see approaching potential preterm babies for this trial in relation to your role as a research staff member? (DOMAIN: SOCIAL PROFESSIONAL/ROLE AND ID)
    - PROMPT: Do you see this as something that is a part of your current role? If not yours, whose?

- PROMPT: Do you think it should be part of your role? Whose role should it be?
- PROMPT: What would be your responsibilities in this position?
- PROMPT: Do you think that the physician/neonatologist should be involved in the consenting process for a new intervention, like MSCs trial?

7. (Ask only if mentioned before) You mentioned earlier a few reasons that might stop you from being able to approach patients for a clinical trial.
   (Ask if no reasons mentioned before) What are some reasons that might stop you from being able to approach patients for a clinical trial.
   How confident are you that you could identify preterm babies on your unit for a potential trial of MSCs if one were to take place in the next 6 months? (DOMAIN: BELIEFS ABOUT CAPABILITIES)
   - PROMPT: What would make you feel more confident?
   - PROMPT: What would make you feel less confident?

8. What are some of the benefits that you see of consenting potential patients for a trial of MSCs for BPD? (DOMAIN: BELIEFS ABOUT CONSEQUENCES)
   - PROMPT: For you, for patients enrolled in the trial (symptoms?), for future patients, for their parents/families, for anyone else, for advancing research,

9. What are some of the disadvantages that you see of consenting potential patients for a trial of MSCs for BPD? (DOMAIN: BELIEFS ABOUT CONSEQUENCES)
   - PROMPT: For you, for your patients, for anyone else. Risks/side effects?
   - PROMT: Other competing clinical trials

Offer to describe possible side effects and negative consequences of the MSC treatment.

10. Do you think the risks outweigh the benefits? (DOMAIN: BELIEFS ABOUT CONSEQUENCES)

11. Do you expect that consenting potential patients for this trial will result in more good things or bad things? PROMPT: In what way? (DOMAIN: OPTIMISM)

12. What are some of your goals of consenting potential patients for this trial? (DOMAIN: GOALS)
    - PROMPT: improving the patient's respiratory status, improving long term outcomes, contribute to a new treatment for preemies

13. Generally, how often might something else be a higher priority than approaching potential patients for this clinical trial? (DOMAIN: GOALS)
    a. PROMPT: Might something be more urgent? What?
    b. PROMPT: How do you think these priorities will impact your ability to approach patients for the trial?

14. What would motivate you to regularly and routinely approach potential patients for a trial of MSCs for BPD? (DOMAIN: REINFORCEMENT)

- PROMPT: Patient benefit, science benefit, clinical care, friendly competition in terms of recruiting compared to my other colleagues as to who recruits most/least; being acknowledged in the academic outputs from this trial?

15. Do you think it is likely that you might sometimes forget to approach potential patients for this trial or follow-up with a potential patient after approaching? When would you most likely forget? What might help? (DOMAIN: MEMORY, ATTENTION, DECISION PROCESSES)
    - PROMPT: reminders?

16. What resources do you need to be made available to you to approach potential patients for this trial? What resources do you already have? (ENVIRONMENTAL CONTEXT AND RESOURCES)
    - PROMPT: neonatologist support, institutional support, financial support
    - PROMPT: What tools might help to help parents understand the trial?

17. Who else's views are important to you when deciding to approach pre-term babies for this trial, and whether you can approach them? (DOMAIN: SOCIAL INFLUENCES)
    - PROMPT: patient's family, neonatologists, colleagues, results of other phase 1 trial about stem cells and BPD

18. How does approaching extreme preterm babies for inclusion in an early phase clinical trial make you feel? (DOMAIN: EMOTION)
    - PROMPT: What emotions come to mind when you think about doing this? And how does that affect your consenting?

19. What are some strategies you would use to stay on top of consenting potential pre-term babies for clinical trials in general? (DOMAIN: BEHAVIOURAL REGULATION)
    - PROMPT: Are there any strategies you have used in the past that has helped you stay on top of consenting potential patients that might help other neonatologists?
    - PROMPT: What can you do personally to help stay on top of consenting numerous potential patients?

We're developing a video to help answer some questions that parents might have when considering whether to enrol their child in the future. We'd love to show you what it look like and then ask you a few questions afterwards. Show MSC animated video

Having seen the video, what are your initial reactions? Do you have any questions or concerns that are not yet answered?

20. Are you comfortable with who presented the information? What are your thoughts about the team that will run the study? (DOMAIN: SOCIAL INFLUENCE)

21. After watching the video, how confident are you to use this tool to help with recruitment? What might make you feel less confident to use this video tool to enrol patients in this trial? What might help you feel more confident to use this video tool? (DOMAIN: BELIEFS ABOUT CAPABILITIES)

22. Are there any concerns or that you can see potentially causing a problem by using this video to show to parents? (DOMAIN: BELIEFS ABOUT CONSEQUENCES)

23. After watching the video, is there anything that is still a barrier to you for enrolling patients into this trial? (DOMAIN: DEPENDS ON ANSWER)

    PROMT: What are the biggest concerns about enrolling patients into this trial?
    PROMPT: Do you think the benefits outweigh the risks of participating? (DOMAIN: OPTIMISM)

24. Would you use this tool to show to each potential patient? (DOMAIN: INTENTION)

    PROMPT: Why/Why not?

    PROMPT: How motivated are you to identify potential patients if the trial's goal was to test the safety of MSCs, but not to test if it improved your patients' health? (DOMAIN: INTENTION)

The interview is over, is there anything else you would like to ask me or comment or final thoughts that might help with recruitment?

Appendix B: Summary of belief statements and sample quotes from participants assigned to domains identified as relevant

Domain	Subtheme	Belief statement	Frequency (out of 14) (n=%)	Sample quote
Knowledge	Knowledge of therapeutic treatment	I am aware of mesenchymal stromal cells	7 (50)	"BPD is not familiar to me as well as mesenchymal stromal cells"-Participant 9
		I am unaware of mesenchymal stromal cells	7 (50)	"I have heard of it but do not have ton of knowledge"- Participant 2
	Knowledge of disease of interest	I am aware of BPD	14 (100)	"At our site we do a lot of BPD studies and stuff like lit reviews, and we look at BPD in relation to pulmonary hypertension"-Participant 8
	Knowledge about recruitment procedures	I need a clear eligibility criteria and trial information to properly screen for this trial	13 (93)	"Some protocols are very detailed and then some lack stuff and so knowing exactly what the patient is going to be going through, so you can give him the full picture. What follow up looks like and knowing more of the nitty gritty things but like."-Participant 9
	Existing knowledge about the uc-MSC therapy	I would like to know more about toxicity, adverse events and expected outcomes	6 (43)	"I think we have to look at the data and look at the most recent studies and if there's preliminary data from Korea or other sites. We have to see how severe the reactions are, how frequent they are, and to what extent it was harmful."-Participant 3
Environmental context and resources	Logistical factors play a role in my recruitment process	Meeting parents on their time may be a challenge	7(50)	"So, my main challenge is just trying to catch the parents when they arrive and sometimes, they arrive in the evenings and I'm not there so that that's like just logistical challenge. It's not a I guess the parent's fault, it's not anyone else. Just yeah, it's just circumstance"- Participant 7
		There may be a language barrier	2 (14)	"Sometimes language barrier if we can't get to a translator, that could be a reason that we miss somebody."-Participant 8
		Due to COVID we work from home	7 (50)	"We work from home. But if there is a potential participant, we will try to meet them in the unit or connect them virtually"
		Nurses time and availability	4 (28)	"For some trials we cannot connect with the parents because the nurse is unavailable. If the nurse is away on lunch break and the fill in nurse isn't sure what's going on, that's another thing that would impede me obtaining consent."- 5

	The need for support and tools	Education for support staff	5(36)	"Anything you could provide like a video to show. Yeah, giving the nurses some Peace of Mind. I you don't want to hurt baby and they don't want to screw up the study. Right, I appreciate that we want to proceed with caution and make sure everything is done right and we don't want deviations"-Participant 11
		Other consenting resources	13 (93)	"Having like these recaps of a study. What it looks like. And they just put all the results of the study. But doing that in the consent format such as a this is a problem, these are the opportunities, this is what is known, and this is the study like in a one in drawing and pictographs" -Participant 5
		There is no need for other consenting resources	1 (7)	"I honestly find that the more information I give to parents, the less they consent."- Participant 6
	Having accessible to tangible information	The animated video is a great tool and accessible	12 (86)	"Having the video is great. Everyone have phones. so, I think that's feasible. And it is not very long, it is a short video."-Participant 7
	Access to funding	Funding is important to keep the study open and moving forward	3 (21)	"So if we were to participate in this study, we would have to talk a bit about what the funding model was and how many patients we would be expected to recruit here. Whether we have the resources available in terms of personnel or we have to hire somebody"-Participant 10
Beliefs about consequences	Perceived disadvantages	Unknown safety and efficacy	11 (79)	"The one concern for me is pulmonary embolism. It isn't really something that we see in these babies, so that might be a bit concerning because that's something That's new to this population for the most part." – Participant 8
		Overwhelming the parents during approach	8 (57)	"So I would suspect that the ones who are on higher levels of ventilation, the parents may not be actually in the mindset to consent to a trial like this unless they're at stage where their lung disease is so severe that they're really willing to try anything"- Participant 14
	Staff workload and stressors	Staff buy-in is a concern	8 (57)	"There is an increased expectation for what we do at the bedside and people are feeling that they're doing a lot already and to ask them to do more, even to monitor righter? This might have an impact on the success of the study right. "-Participant 4
		Staff buy-in is not a concern	3 (21)	"I our bedside staff are quite very willing to participate in studies. Obviously depending on the day. I definitely think it would be more workload, but not in an overall matter like I like a one day we we've done studies that were, you know, a one hour long study. And yes, it was more workload for that day. But it was the overall benefit was outweighed the workload." -Participant 12

		Conflicts with other multiple active sites within the unit	3 (21)	"Some of the challenges are that if there's a large number of studies going on at once, our consent window, I guess, is 14 to 21 days of life. And sometimes parents have been approached by a lot of different teams before I kind of come in." - Participant 2
		Multiple active studies within the unit are not a concern	8 (57)	"Most parents actually didn't mind being approached with multiple studies. They like having the flexibility to just sort of pick and choose what they'd like to participate in."-Participant 6
	Treatment benefits	I believe there is a lot of benefits with the MSC administration	9 (64)	"I think definitely it would be beneficial for the infant themselves if they could have an improvement in their lung function and so their risk of BPD would decrease or even the severity would decrease like that's huge for preterm infants because that is like the major risk factor, chronic illness that they deal with for their whole life and then that would benefit the parents so that they wouldn't be as they wouldn't have such a sick child"- Participant 5
	Long-term benefit	Advancing scientific research	13 (93)	"Clinical trials in neonates are lacking, and I think it's really important that this community gets involved in more multicenter initiatives such as this. You know giving access to patients to, the most current therapies available advancing scientific knowledge is everything." Participant 10
Beliefs about capabilities	Confident	I feel confident in my ability to screen/ recruit patients for this study	11 (79)	"I would still feel comfortable. I think because I could speak to the earlier phase to give some confidence and some credibility to the study and to give rationale that we're continuing to build on the knowledge we've already have" -Participant 11
		I feel confident in my ability to screen/ recruit patients for this study with the use of the video	12 (86)	"The video I think it brought everyone to the same mental model instead of them, sort of figuring it out in their head. So video is very helpful, and I would use it for sure."- Participant 4
	Not confident	I am not confident in my ability to enrol for a Phase 1 trial	1 (7)	"Honestly, it makes me feel a little bit hesitant just because it is such a new therapy. And like you said it's phase 2, so it's really early on so it makes me a little hesitant in the fact that I don't know the adverse outcomes."-Participant 5
	Variability of screening roles	Neonatologists should be involved with the consenting process	11 (79)	"Some form of neonatologist might be helpful to be involved, or like a fellow doctor for answering questions. The physician caring to the baby should be involved."– Participant 2
Goals	Motivators	Approaching parents is my priority	9 (64)	"For us, consenting takes priority like we do that first, and then everything else is the fillers in amongst getting patients. For one study we come in on the weekends to consent patients because it's a quick turnaround because we're trying to catch moms on the postpartum floor. So yeah, we come in lots to try and accommodate that."- Participant 6

		I have other competing priorities	7 (50)	"We have to prioritize studies on the unit where those that have the greatest therapeutic benefit for patients or prioritize. "- Participant 10
		Reaching recruitment goals	3 (21)	"I don't like failing. I want to hit a recruitment target. I'm always looking for Okay, like, how many have we recruited this month? What if my barriers been? How can I either refine my approach or refine when I'm going to maximize those number of families?"-Participant 2
	Advancing science	Approaching patients is important to contribute to this field	12 (86)	"Well I want to be part of this because advancing respiratory care is a huge thing. BPD is a high rate in Canada, wanting to reduce that would be. Amazing on for the overall benefits of future babies and the baby that we're treating right."- Participant 12
Intention	Intent to participate	I intend on approaching parents for this trial	14 (100)	"I think if the phase one was done and we had information that showed success or if you reached your primary outcome, which is the safety, feasibility and so forth. I will definitely approach parents"- Participant 4
Behavioural regulation	Coping plans	I use list to keep track of approached/ consented patients	7 (50)	"We have the patient list That's on epic, and that's what's used for screening, so they would review that daily. And every time there is a patient who is approached. we use Epic the research notation to identify that they've either been identified, screened, consented, there in the process of being approached" -Participant 10
		Alternative plans when approaching parents with multiple trials	5 (36)	"Part of their mandate is to discuss competing studies and how those will be managed. So studies are prioritized based on the therapeutic benefit and the risk profile." -Participant 10
		Recruitment plans to avoid missing parents	3 (21)	"We've sort of worked out a mechanism, if you will, where I'll keep my PI and a few other people involved in our research team and involved are informed so that if I can't approach and it's time sensitive, someone else will then sort of carry the torch if you will"- Participant 4
Skills	Approaching skills	Building relations with parents	9 (64)	"We're telling the families that we're an academic center. We do active research and that if it wasn't for research, we would know some therapies work right. We also tell them at any time they can leave the study. Really trying to get their trust"- Participant 3
	Formal training	We have the formal training	6 (43)	"I was trained by a research nurse, a respiratory therapist, and the PI on the study, so kind of a combo of all three, depending on who is available." Participant 2
Nature of Behaviour	Current and past experience	Approaching parents for past trials went well	9 (64)	"My comfort in approaching families and speaking to them about the study is based on I think, the years of experience I have being in a critical care environment and being able to look beyond a lot of the environmental sort of distractors, if you will. But as well, I've had a fair amount of experience in

				communicating and speaking with families with my clinical background."- Participant 4
		I achieve the required recruitment target	7 (50)	"We do pretty well. We get a reasonable amount of yes's compared to no's. I think we've perfected our consenting process pretty good. We do a good job at informing our patients."- Participant 9
		Recruitment window	3 (21)	"The more difficult studies are the ones to recruit on day zero. I think you know, with the stress of delivering premature baby and then having to talk to parents about a study during that time I think plays a part in a lot of them refusing consent… I usually know where the mom is, and we meet in her room or make an appointment to meet. I usually try to get consent at the bedside." – Participant 13
Social Influence	Support from colleagues	Opinions of other colleagues' matter before approaching patients	8 (57)	"What's key is that we educate nurses during their mandatory education days right now, because families have struggled when they've consented to a study, and then the nurses aren't aware of what's going on. Or, you know, aren't even aware that the study is happening. Educating the bedside nurses and what's going on can really, really add to the success of consenting" -Participant 13
Memory, attention, and decision process making	Memory	I will not forget to approach a parent	5 (36)	"Every day I'm spending every day and if I recruit someone, I'm going to screen it every day for eligible patients, and I have the responsibility for that and try not to forget that"- Participant 5
Optimism	Optimism	I would expect more good things than bad	4 (29)	"I hope so. We are at this phase of research because it's based on information already that provides us with hope"- Participant #7
Social/ Professional Role and Identity	Perception of recruitment role	It is our role to recruit patients	9 (64)	"my comfort level to approach families is good, because that's currently part of my job now. And my role, and I feel I can speak fairly easily, even with the questions that many of them have come back to me about."-Participant 4
		I oversee recruitment	4 (29)	"I have a research assistant usually does recruitment and I oversee"– Participant 10

Appendix C: Subthemes and Belief Statements

Most Relevant Domains

The most relevant domains were identified based on the criteria outlined by Atkins et al. (2017). Relevant domains were chosen based on the frequency with which beliefs and themes appeared in each domain, the presence of conflicting beliefs, and perceived relevance to the target behaviour.

Domain	**Number of participants represented**	**Total number of instances coded to domain**
Knowledge	14	42
Environmental context and resources	10	42
Beliefs about consequences	13	44
Beliefs about capabilities	8	18
Goals	12	37
Intention	14	23
Behaviour regulation	7	14
Nature of behaviour	9	41
Social influence	8	28
Skills	9	30
Memory, attention, and decision making	5	7
Optimism	4	6
Social and professional role and identity	13	57
Reinforcement	0	0
Emotion	0	0

Knowledge

N = 14

Knowledge of Disease and Treatment

All participants (n = 14) were aware of Bronchopulmonary Dysplasia. In fact, many expressed that their unit focuses on respiratory research.

> R: Yes, I am very familiar with BPD. So most of my studies are usually pretty respiratory centric or recess. Our hospital does high risk deliveries, and we have a lot of preterm birth, so a lot of our studies are also recess focused as well.
> *Participant #8*

When asking about the MSC treatment, half of the participants were aware of the treatment (n=7) In fact one participant indicated keeping up with Dr. Bernard Thébaud's research.

> R:I am familiar with MSCs because I follow Dr. Thébaud's journey and excited to see what he is planning to do in the future with these cells.
> *Participant # 9*

The other half were not aware of the treatment but despite their perceived lack of knowledge, they were still optimistic about the trial. One participant mentioned being aware of the mechanism of the cells before speaking to potential participants.

> R:I have not heard of this cell before but keen to learn more. I would like to know the science behind the stem cells as therapy for various treatments, I would have to know more about the proposed mechanism, the proposed therapy before I would feel comfortable to speak to a family about that.
> *Participant #14*

Recruitment Procedures

Most participants (n = 13) indicated the need to know more information about the treatment discussing the importance of having a clear eligibility criterion in the protocol and the different procedures involved with the trial. Recruiting involves additional behaviours that that influence the approaching of parents.

> R: Having a detailed protocol describing the procedures and knowing which babies we need to recruit. I read the protocol and I digest it before approaching parents. I prefer to go through the like the protocol or consent form. OK, So I know what I want to say to the parents
> *Participant #1*

Existing knowledge about the MSC treatment

Participants (n=6) identified having a clear idea about how safe and invasive the treatment is very important. Especially, the expected outcomes, thus when telling parents about the trial, there are clear expectation.

> R: How would you be able to say, if you had a clinical event happen? How would you know it could be that versus just the normal trajectory of their illness or pathology, most of these babies will have an element of RDS. And if they have a change in clinical status, the question would be, is it because of our therapy as a possible AE? What would the expected outcomes be?
> *Participant # 4*

Environmental Context and Resources

***N* = 10**

Logistical factors

Several participants (*n* = 7) discussed the availability of the parents impacted their ability to recruit participants. For some research personnel's, mentioned that some parents come after working hours or weekends and those parents are considered missed.

> R: My hours don't line up with some of the hours that the parents come, and they'll come in evenings and I'm not here in the evenings, so those are the only difficulties I'm having now, but in the past, I didn't have any difficulty recruiting patients.
> *Participant #5*

Other mentioned that there may be a language barrier with the parents (*n*=5) and there are limited options to connect with them and may be a reason to miss an eligible participant.

> R: Parental language barrier is one. We have a very diverse patient population here and we do have access to interpreters. But sometimes it's hard to coordinate like sort of when the interpreter can be there for medical reason and for research reasons. So that's one thing.
> *Participant #6*

Seven participants (*n*=7) also mentioned that since the pandemic they work from home. Instead of regularly checking the units for eligible participants they must rely of the nurses or the parent's schedule to decide when to come in to approach or even virtual consent.

> R: Since the pandemic started, I work from home. If I'm lucky I get to be in my office once a week. So that that is a factor. So, we will miss some kids if I don't decide to mee the parents.
> *Participant #11*

Four participants also mentioned that they must coordinate with the nurses before approaching parents. The availability of the nurses will impact they decision to speak with a potential participant.

> *R:* For some trials we cannot connect with the parents because the nurse is unavailable. If the nurse is away on lunch break and the fill in nurse isn't sure what's going on, that's another thing that would impede me obtaining consent
> *Participant #5*

Additional support and tools

The need for education of the study was mentioned by five participants. Training materials, regular communication were some things that were mentioned to educate the clinical staff, including the nurses. Thus, having slide decks and even a short video to explain the study conduct may influence trial participation.

> R: The only thing I can think of offhand might be the training materials for the bedside stuff. The preparation of you knows, a slide deck or a video or something to help facilitate that.
> *Participant #10*

One common factor was the additional consenting resources were required to help parents understand the study. Having the consent form alone can be intimidating for parents. Many participants (*n*=13) said they need resources that can facilitate their discussion with parents.

> R: Pamphlet might be nice. The consent form is not as approachable, that they may not be able to communicate back. So, something like a lay pamphlet to really discuss what it is, what the benefits are, what the risks are just a very kind of quick summary that's more approachable, then the long, six, seven page consensus to give would be good.
> *Participant #2*

Although one participant did mention that they more information you give to parents the more likely they will day no

> R: Like, even with the additional pamphlet or things like that they're not in the right headspace to understand and most likely pass on the study.
> *Participant #7*

When asked about the animated video to be used as a consenting tool, many participants were enthusiastic that this was available for parents (*n*= 12).

> R: I think the video is a great idea. But yeah, like something to leave with the patients or email to them like we're starting because of COVID, we're trying to do a lot more electronically
> *Participant # 13*

Funding

A related concern voiced by 3 participants had to do with available funding to support the trial. They mentioned compensation for recruiting participants, submitting ethical documents, coordination with other staff and for variety of procedures including blood and trial related treatments

> R: Having support for anything that has to do with regulations and access to the product. If you must do biomarkers and blood sampling, having support for that person and on that chain of custody of the product or of the product in and of any sampling is going out, so that's going to be a lot of time for the local investigator to be hopefully supported in those tasks
> *Participant #3*

Belief about Consequences

***N* = 13**

Perceived Disadvantages

Many participants mentioned the uncertainty of the risks of the cells (*n*=11). After viewing the video, many pointed out the risk of pulmonary embolism and although after reassuring them that the risk is low, they were still wary of the treatment. Few also mentioned safety of the cells and if they are safe to give it babies.

> R: where the challenges we've had with clinicians is when we are using new drugs and there are potential side effects to it, right? That will be the biggest thing. So when will go over the study criteria, the design I think there's going to be a lot of concerns for mesenchymal stem cells. If you're using the actual cells. It's not the same as using the medium.
> *Participant #3*

Eight participants also mentioned that approaching the parents while they are under huge amount of stress is a challenge, especially for recruitment of an early phase trial.

R: I mean like premature babies, a lot of high stress situations, so sometimes I do approach parents and within the first sentence I can tell this is not going to go well. That's I think those are like the main big limitations with any clinical trial that I have done.
Participant #7

How well toxicity and side effects are managed may potentially influence the researcher's screening assessment and decision regarding patient enrollment. It will be important to demonstrate to the clinician team that toxicity management guidelines are evidenced-based and well-reasoned. Furthermore, with our recruitment window, it gives the researchers time to approach parents and evaluate the situation before speaking to parents. Providing tools such as the video may help with their consenting process

Staff Workload and Feasibility

Staff buy-in was of great concern to as least 8 participants. Many suggested that having the nurses on board will aid in approaching parents. However, since nurses have a high workload, adding more on to their hands may cause some tension. Three participants did however mention that their unit works as a team and once seeing the value in the research, most clinical staff are on board.

R: If there are significant adverse events or if something happens, that may change the mood, if you will be not just the patient, population, family, but also the healthcare teams. If they're seeing that it's not working, or they have concerns around the validity that may jeopardize future buy in difficult
Participant #4

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R: In my experiences in the past, we've done studies. I find that the nurses who are looking after the study patients do tend to be a little more involved, even though it might be a little more workload, and, in the end, they seem a little more involved in the care of those patients and a little more invested
Participant #13

Another concern that was voiced out was other competing studies in the unit (*n*=3). There may be difficulty when approaching parents with multiple studies. One staff member noted that prior studies will be given priority for recruitment.

R: We're going to respect our prior engagements, so it's not about priority of a study. It's about respecting our commitments to current studies.
Participant #3

Although eight have said having other studies in the unit will not impact their recruitment as the recruitment window gives them the flexibility to approach parents as well as the different methods implemented to deliver of the trials to parents.

R: There is many ways to approach it to increase participation really, right?
And I don't find that families shy away from consenting just because they're in another study. They shy away because of the balance between wanting to protect their baby, and understanding the information
Participant #14

Perceived Benefits

Participants identified treatment benefits as the primary positive outcome of having patients participate in this trial. The majority (n = 9) indicated that this trial is beneficial because it offers a lot of promise to patients and help decrease the rate of BPD. Many (n= 13) voiced out that it will help advance gene therapy research in the field especially with this ultra-rare disease which is overlooked by the industry.

> R: I think if it helps improve the rates of BPD. I mean that's the most exciting thing because you know, I have seen the results of chronic lung disease and stuff. And I know how frustrating it is when there is no real treatment for it.
> *Physician #6*

> R1: personally, I think it offers a lot of promise. I think it's more for future babies, and certainly for informing future research, projects, and ideas
> *Physician #4*

As suggested by these two quotes, the research staff expressed a lot of hope and excitement for the therapy. Their motivation was primarily focused on being part of a trial that can help treat babies from BPD.

Beliefs about Capabilities

***N* = 8**

Of those who were coded into this domain, eleven indicated that they would be confident in screening and recruiting patients for an uc-MSC clinical trial.

> R: I think it would be fine on my own though, like maybe like this would be easy consenting
> *Participant #7*

After showing the video as a consenting tool, most (n=12) indicated that they would feel more confident to approach parents. In fact, one participant said that the video will be great to show to parents to give them a good picture of the trial in comparison to the consent form.

> R: The video I think it brought everyone to the same mental model instead of them, sort of figuring it out in their head. So video is very helpful, and I would use it for sure.
> *Participant #4*

Although with the tools and the study documents provided, one researcher mentioned they are not confident to screen for an early phase trial because of the risks associated.

> R: Honestly, it makes me feel a little bit hesitant just because it is such a new therapy. And like you said it's phase 2, so it's early on so it makes me a little hesitant in the fact that I don't know the adverse outcomes.
> *Participant #5*

Eleven participants described in tandem with the clinical research team the lead investigator and or the attending physician should help with recruitment with clarifying any questions the participants may have. The research staff will do the initial approach and provide details of the study and obtain the consent.

> R: Maybe the PI should be involved, or some form of neonatologist might be helpful to be involved, or like a fellow doctor for answering questions. The physician caring to the baby should

be involved. The families are very interested in how this will affect the overall care of the baby, right? And that is more clinical
Participant #12

Goals

***N* = 12**

Researchers were primarily motivated by their role to consent patients as well as help benefit future patients. Nine participants expressed they were motivated to approaching parents because that is what their task for the day.

> R: my priority for the day is to make sure that they get approached, and then anything else, you know, prioritized in order that it needs to be.
> *Participant #2*

Majority (*n*=12) were motivated to consent parents to advance respiratory care for babies and indicated that screening for this clinical trial was important because it added to their knowledge base and provide better safety data.

> R: Early evidence from the studies I'm involved in where there is a correlation between BPD and brain development and growth. So, if we could reduce the incidence of BPD, that would be great for brain. And if the study that you're speaking of MSCs for BPD did that. So, I think it would be to, you know, improve long term pulmonary outcome
> *Participant #4*

Three participants also expressed being motivated to reach their recruitment goals

> R: I have a recruitment number that I like to get. You know, I feel accomplished if I reach my target.
> *Participant #7*

Seven expressed general support for the trial but other competing clinical trials will take precedence when approaching parents.

> R: If I know that a study in our unit is going to expire soon and still requires like three or four babies, then that would take priority over this study. So it just depends on the timeline, right? So, like, but if this study is going to expire soon, then of course like I'm going to ramp up the efforts to try and recruit more patients. So that's the only thing that would get in the way other than.
> *Participant #5*

Intention

***N* = 14**

When asked whether they will participate in this trial to recruit parents, most (*n*=14) intended to participate. Those that said they would, cited reasons such as wanting to offer parents hope with the treatment option and wanting to contribute to the evolving science and technology for rare disease.

> R: the stem cells itself is not something I'm as familiar with, but I'm happy to kind of master that that area as much as I can to be able to approach and to be able to answer questions, but I think it's great.
> *Participant #2*

Behavioural Regulation

***N* = 7**

When asked about their strategic plans to approach parents, few (*n*=7) mentioned having lists to keep track of participants that have been approached or who are eligible to be approached. Three also mentioned having plans in place to avoid missing parents by communicating with the research until constantly to ensure someone if available.

> R: Excel spreadsheet that I have in that like kind of indicates yes, no pending consents.
> *Participant #7*

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> R1: The first person in the unit will usually go through the list and if a patient is eligible, we would communicate with the nurses to page us if the parent is in unit. We would call the nurses throughout the day to ensure we don't miss any
> *Participant #9*

Five participants mentioned coping plans when there are multiple studies within the unit. Few strategies include prioritizing studies that have the most benefit, telling families that they will be approached for multiple studies throughout their NICU stay and or take one study per population

> R: Our plan is to do only one study per kind of population. Like if we chose to do yours trial I you know we would make sure that there's nothing else that's overlapping.
> *Participant #9*

Nature of Behaviour

***N* = 9**

All of the participants have recruited participants for research studies. Nine have suggested that because of years of experience, recruiting for a stem cell trial will not be difficult. Three participants mentioned having time pressure can influence their recruitment rate. Moreover, seven participants stated that they usually meet their target recruitment goals for their studies regardless of any hardships. This is reassuring for our team to know that other researchers are capable to recruit for an early phase study.

> R: It usually goes quite well. I mean, I think we usually end up having, like you know, the average number of parents refusing consent. We've always been able to, to at least reach our target numbers though.
> *Participant #9*

Social Influence

***N* = 8**

Researchers approaching behaviours were primarily influenced by their colleagues (*n* =8). How and when the research staff approach potential participants depend on buy-in from other clinical staff. The common point mentioned that other physicians and nurses should understand the importance of the research which will facilitate the consenting process.

> R: One of the neonatologists was not keen on us approaching parents for whatever reason, whether we thought it was valid or not. I just abandoned it. If they were aware about why this study was being done, the outcome may have been different.
> *Participant #8*

Once the trial is accepted, participants noted that they need the opinions from their colleagues before considering enrolling a patient into the study.

R: I would consult with genetics and respirology. To see what the likelihood that the child's going to be eligible. We need to be all connected.
Participant #10

Skills

***N* = 9**

Participants indicated that they have received some type of formal training (*n*=6) prior to approaching parents. Many institutes have requirements that researchers must meet before speaking to parents. Three participants also mentioned that they had mentors to teach them about ways to approach parents.

R: I had just a week of overlap with the previous research assistant and then our coordinator went on medical leave, so I basically taught myself a lot of things just at the start and so yeah. A little bits and pieces everywhere, I guess.
Participant #7

Another common theme that many of the participants mentioned was building relations with parents when consenting them for a trial. Nine expressed assessing the environment prior to speaking to parents and not overwhelming them with tons of information.

R: Giving a general overview and trying to explain it simply because, of course, when you're throwing out kind of big words, big phrases, it can be a lot for them.
Participant #2

Memory, attention, and decision making

***N* = 5**

Memory

Participants were asked whether any factors in their environment might cause them to forget to consent a patient. Five participants responded that they were unlikely to forget given the importance of the trial, and that is their role. Given the concerns over recruitment feasibility, ensuring no patient is missed and forgotten will be an important strategy for the success of the trial.

I: Do you think it's likely that you might forget to approach a potential patient for this trial.
R: I don't think there was a time that I forgot to approach a parent.
Participant #13

Optimism

***N* = 4**

Of the participants that responded, four were optimistic about the trial and expected more good things than bad from the trial results. One participant stated that anything to decrease the incidence of BPD is a good thing.

R: Spent the last 30 years seeing what BPD does to these babies. Very different when you're a parent and this is your brand-new baby and if the risk will be worth it to them?
But to me yes. Just really, the end of the day, their lungs that are not mature enough to be born, so prematurely.
Participant #11

Social/Professional Role and Identity

***N* = 13**

Participants (*n* = 9) stated that recruitment for trials was part of their role. Some noted that they have clinical research unit, and everyone partakes in the recruitment procedure. Four researchers stated that they oversee recruitment and step in if one of the researchers needs help.

> R: I support the research staff here. I'm not directly involved in recruitment for the most part, but on occasion I might step in if in the event there's a staff member who's absent, for example. *Participant #10*

Chapter 4: Is Adeno-Associated Viral Vector the solution to treat Surfactant Protein B Deficient Babies-A stakeholder interview study with physicians to optimize a gene therapy trial in neonatal babies

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Abstract

Background: Novel therapies often fail to reach clinical practice due to low recruitment rates. Prior to conducting the first adeno-associated viral (AAV) vector trial to treat surfactant protein-B deficient babies in the world, we aimed to identify physician-related barriers and enablers, to screening and recruiting patients, for an early phase gene therapy trial.

Methods: We used the Theoretical Domain Framework (TDF), a framework used to identify barriers and enablers to behavior change, to construct interviews with Canadian, American, European, English, and Scottish physicians (neonatologists and pulmonologists). We used direct content analysis to identify relevant domains reflecting the key factors that may affect screening and recruitment

Results: In total, we interviewed 18 physicians, comprised of 13 neonatologists and 5 pulmonologists. Though physicians were optimistic about the trial, key barriers identified by physicians include safety, feasibility, and the expected outcomes of the treatment (domain: Knowledge and Beliefs about Consequences). However, many physicians believed that the AAV gene therapy treatment would benefit SP-B affected babies. Physicians expressed that a clear study protocol is necessary to screen babies; they indicated that they could screen, regardless of the concerns with respect to workload stress, extreme rarity of disease, and different institutional clinical care practices (domain: Knowledge, Emotion, Goals, Beliefs about Capabilities, Beliefs about Consequences, and Intention). They also noted the additional resources required to execute this trial including additional funding for staff, support to obtain regulatory approval, and providing diagnostic tools that is not part of standard of care (domain: Environmental Context and Resources). Many expressed the need for support from clinical professionals prior to approaching parents and highlighted variability in screening roles (domain: Social and Professional role/ Identify and Social Influence)

Conclusion: The application of the TDF helped identify key potential barriers and enablers prior to executing one of the first AAV trials in babies. The results will help to refine the study design and execution. This approach can optimize trial procedures and help other clinicians with their early phase gene therapy trials.

Introduction

Surfactant is a substance in the lungs that helps lower surface tension inside the alveoli, which supports the passage of oxygen[1]. Lack of surfactant in the lungs can cause interstitial lung diseases[1]. Surfactant is composed of four protein types, surfactant protein(s) A-D [1]. Surfactant protein B (SP-B) is of interest in congenital surfactant protein disorders [1]. Infants with genetic mutations in the SFTPB gene lead to abnormal function of surfactant secretion leading to fatal lung disease[1]. Although it is reported that there is a 1 in a million chance of having this mutation, infants with inherited deficiency of SP-B have no other current treatment options other than lung transplantation[2]. In fact, full-term infants with this disease show rapid respiratory failure and death within the first 3-6 months of life without lung transplantation[3].

Our lab has shown preclinical evidence that the use of a novel treatment option, adeno-associated viral (AAV) vector, mediated gene therapy may be the solution to help prolong survival until donor lungs are available or even cure the disease [4]. Intratracheal administration of the vector carrying a healthy copy of the SFTPB gene restores surfactant homeostasis, prevents lungs injury, and improves lung physiology[4]. When planning a clinical trial, especially for rare diseases, ensuring feasibility is of great importance. The rate of discontinuation for trials involving rare pediatric diseases is 30.4% due to funding issues and low patient accrual[5]. Many therapies fail to reach the bedside due to delayed recruitment and or low recruitment rates [5]. A systematic review identified factors that lead to low recruitment difficulty with the consent procedures, lack of time and training materials for medical staff[6]. Engaging with patients and physicians may help to overcome barriers to trial recruitment. Other early phase trials, such as the mesenchymal stromal cell trial to treat bronchopulmonary dysplasia in neonates, identified barriers to trial participation however, there is very little literature regarding pediatric based early phase gene therapy trials[7]. To our knowledge, there is no trial using AAV to treat SP-B deficiency. Caution must be taken because many studies have been carried out in animal models, however, low number of studies proceed to clinical trials[8]. As of today, there are only two FDA approved AAV-based gene therapies[9]. Majority of the trials focus on using the vector to treat ophthalmological and neurological diseases in the pediatric population[9,10]. Recruitment by clinicians in a gene therapy trial depends on many factors; exploring and understanding these factors may help us construct a more robust trial design to optimize trial execution, recruitment, and completion.

Identifying and addressing recruitment barriers in advance of trial launch can help to optimize trial recruitment[11,12]. Success of this AAV gene therapy trial depends on the neonatologists and pulmonologists willingness to identify and refer eligible patients to the trial. Previous findings have identified barriers that undermine trial recruitment with physicians. These include physician attitudes towards the trial[13,14], available time and resources[11], treatment preferences[11], challenges with the informed consent[15] process as well as explaining the trial concepts[16]. Less is known about challenges faced when conducting gene therapy trials, as it is new to the field. It was imperative to identify and address potential barriers that could impact the success of this trial prior to the launch. Thus, in preparation for a clinical trial with the use of AAV to treat SP-B deficient babies, we sought to identify barriers and enablers of physician participation with the use of the Theoretical Domain Framework (TDF). The TDF is a qualitative framework that can be used to identify barriers and enablers to clinical trial participation. We used this same technique to understand barriers and enablers to physician involvement in a trial of MSCs to treat

bronchopulmonary dysplasia in extreme premature babies[7]. The TDF synthesizes the constructs from 33 behavior change theories into 12 domains. The TDF was later validated and refined in 2012 to include two more domains, totaling 14, to explain behaviour (Table 1)[17,18]. The flexibility and direct links to factors known to affect decision-making and behaviour, are some reasons why researchers use this framework[18,19]. Using a comprehensive, qualitative interview approach, we applied the TDF to investigate barriers and enablers that would influence physician participation in a gene therapy clinical trial to treat babies affected with SP-B. Based on the identified barriers and enablers screening patients for a AAV trial, we will be well prepared to make recommendations on how to optimize support, resources, and training to promote recruitment to an early phase gene therapy trial.

Table 1. Theoretical Domain Framework domains and associated definitions

Domain (TDF-V1)	**Domain (TDF-V2)**	**Definition** [17]
Knowledge		Existing procedural knowledge, knowledge about guidelines, knowledge about evidence and how that influences what the participants do
Skill		Competence and ability about the procedural techniques required to perform the behaviour
Social/professional role and identity		Is the behaviour something the participant is supposed to do or someone else's? (When discussing 'we'/the collective) Boundaries between professional groups
Beliefs about capabilities	**Beliefs about capabilities**	Perceptions about competence and confidence in doing the behaviour
	Optimism	The confidence that things will happen for the best or desired goals will be attained
Beliefs about consequences	**Beliefs about consequences**	Perceptions about outcomes and advantages and disadvantages of performing the behaviour or pervious experiences that have influenced whether the behaviour is performed or not
	Reinforcement	Increasing the probability of a response by arranging a dependent relationship, or contingency, between the response and a given stimuli
Motivation & Goals	**Intention**	Conscious decision to perform a behaviour or a resolve to act in a certain way
	Goals	Priorities, importance, commitment to a certain course of actions or behaviours intentions
Memory, attention, and decision making		Attention control, decision-making, memory, i.e. is the target behaviour problematic because people simply forget?
Environment context and resources		How factors related to the setting in which the behaviour is performed (e.g. people, organisational, cultural, political, physical and financial factors) influence the behaviour
Social influences		External influence from other people, views of other professions, patients and families, doing what you are told and how that influences what you do
Emotion		How feelings, affect (positive or negative) may influence behaviour
Behaviour regulation		Anything aimed at managing or changing objectively observed measured actions
Nature of Behaviour		Relates to the history of the behaviour, and one's experience with said behaviour

Methods

The study was approved by the Ottawa Health Science Network Research Ethics Board and CHEO(20210170-01K). Verbal informed consent was obtained from all participants, and all procedures followed were in accordance with institutional guidelines.

The consolidated criteria for reporting qualitative research (COREQ) reporting guideline was used for this study[20]. The checklist guided the research methods, findings, analysis, and interpretations[20]. We used the validated version of the TDF to frame the interview guide and kept the domain that was removed from the validated version (nature of the behavior) because it captures unique information helpful in understanding participant experiences with screening behaviors [17]. The 15 domains used in this study are presented in Table 1. The guide was developed in collaboration with a health psychologist (JP), NICU physicians (BT, NS), as well as experts in rare childhood diseases (LN,BP). We worked with physicians to identify who must do what differently, in what context and likelihood of recruiting patients with this ultra-rare disease. Thus, we designed questions to explore barriers and enablers to physicians screening and identifying SP-B patients The behaviour of interest was defined using the Action, Actor, Context, Target, Time (AACTT) framework (Table 2) [20]. See Appendix A for the detailed of the interview guide

Table 2. Action, Actor, Context, Target, Time[20]

Action	Screening/ identifying for to a planned future gene clinical trials
Actor	Neonatologists and pulmonologists in Canada, Germany, UK and US
Context	Neonatal intensive care unit
Target	Suspected babies with genetic surfactant metabolism disorder
Time	Day of life 7-14 ventilated

Snowball sampling was used to identify Canadian, American, European, British, and Scottish physicians (neonatologists and pulmonologists) to participate in the interviews. We asked each participant to identify additional colleagues that may offer differing views.

Master's student (KS) with background in health science was trained in conducting interviews and using the TDF to inform data collection and analysis. The research assistant conducted all interviews by Zoom. Sample size was determined using a 10+3 stopping rule[19]. Saturation is an indicator of quality and trustworthiness in qualitative research. Thus, data was considered adequate (thematic saturation) if no new themes emerged within the last three consecutive interviews[20].

During the interviews, participants were encouraged to expand on their answers. At the beginning of the interview, the research assistant explained to the physicians about the upcoming early phase multicenter gene therapy trial to treat SP-B deficient babies. The participants were asked to imagine they were approaching eligible patients for this study and to respond to hypothetical questions regarding potential barriers and enablers to screen potential participants.

KS explained the main goal is to understand if this trial is feasible to execute. All interviews were recorded, transcribed and anonymized.

Data analysis

Using NVivo 12 (qualitative software), a directed content analysis was conducted[21]. Recordings were transcribed and verified by interviewer (KS) prior to analysis. The analysis involved the following steps consistent with standard recommendations for TDF-based qualitative studies:[17–19] (1) coding, which represents linking participants' responses to theoretical domain using a codebook, (2) generation of specific belief statements, which involves grouping a set of responses reported by different participants with similar underlying ideas and/or beliefs, and (3) identification of key theoretical domains [22].

Code book development and coding to TDF domains

The first two interviews were independently double-coded, and the two coders compared coding to develop a coding book. The code book was developed to maintain coding rule transparency and help code the rest of the remaining interviews. Analysis was led by a primary analyst (KS) who coded each interview and allocating relevant experts into one of the theoretical domains[17,19,25]. A secondary analyst (GC), blinded to the primary researcher's coding, subsequently coded the excerpts to the TDF domains. Conflicts were resolved through discussion. Using the code book, the next two interviews were independently coded, Assessment of inter-rate agreement using Kohen's Kappa was conducted for the second two interviews; a priori it was planned that if kappa inter-rater agreement scores did not reach threshold (0.80), single coding would not occur for the remainder of the interviews[23].

Coded data excerpts were converted into belief statements (KS) and revised by a health psychologist (JP). To document the progression from data excerpt to subtheme, we created belief statement tables showcasing subthemes, belief statements, exemplary quotes, case counts (number of participants endorsing a belief) and total frequency count (how many times a belief appeared in the data set). We identified key domains according to frequency of beliefs, presence of conflicting beliefs, and relevance of recruiting behaviour [19].

Results

Participants

Eighteen physicians (14 men and 4 women) agreed to participate in research hospitals from Canada, America, United Kingdom and Europe. Five were pulmonologists and 13 were neonatologists. We approached 76 physicians with an information sheet sent by email and 18 agreed to participate. Interviews were conducted between May and June of 2021 and the interviews lasted a duration of 11 and 42 minutes (median, 24.5 minutes). We focused on neonatologists and pulmonologists because they are the ones that will diagnose and treat these SP-B patients.

Interviews were conducted over Zoom, an online conference platform. Six participants were based in Canada, 5 from the United States, 3 from Germany, 1 from France and Belgium and 2 from the United Kingdom. Nevertheless, every physician reported coming across a patient diagnosed with SP-B, ranging from seeing 0-3 cases (median=1) in their entire medical career. In addition, physicians were questioned about their prior research experience, either as a site

investigator or as a research assistant. Thus, every participant was potentially positioned to engage in specific recruitment activities under the study. Participant characteristics are described in Table 3.

Table 3 Sample characteristics for physicians (n=18)

Characteristic	**n=18 (%)**
Profession	
Neonatologists	13 (72)
Pulmonologists	5 (27)
Gender	
Male	14 (78)
Female	4 (22)
Experience in research	
0-20 years	2 (11)
>20 years	16 (89)
Location of physician	
Canada	6 (33)
United States	5 (28)
Germany	3 (17)
France	1 (5)
United Kingdom	2 (11)
Belgium	1 (5)

Inter-rater reliability

Data from research personnel were analyzed together and consisted of 43 belief statements across 13 domains (Table 4). The first four transcripts were double coded by two researchers; kappa inter-rater agreement scores for the four interviews were 0.93, indicating agreement and that interviews could be reliably coded into respective domains[23]. The remaining transcripts were then single-coded (KS).

We identified seven relevant domains: Goals, Beliefs about Capabilities, Social Influence, Knowledge, Beliefs about Consequence, Social and Professional Role and Identity, Environmental Context and Resources, and Intention. A comprehensive list of detailed belief statements and subthemes associated with each domain are shown in Table 4. In depth analysis of the belief statements can be found in Appendix B.

Table 4. Summary of belief statements and sample quotes from patients assigned to domains identified as relevant

Relevant Domain	Subtheme	Sample belief statement	Sample quotes
Key theme 1: Cautious Hope			
Knowledge	Existing knowledge about AAV therapy	Required education on the product (3)	I would need knowledge of the logistics of the AAV production and storage- Participant 5
Beliefs about consequences	Treatment benefits	The trial will benefit the patients that have no other treatment option (15)	"Basically, we have no treatment. The outcome is very poor, and I would be very positive about a new treatment that might offer help. They really haven't got very much to lose. I'd be strongly in favour."- Participant 7
		Unknown safety and efficacy (8)	"I think there would be potentially concern of causing an immunological sort of response. Then would the babies then require more oxygen or respiratory support? I think that would be the biggest concern." – Participant 5
Key theme 2: Physicians feel capable to screen but require clear study procedures and outcomes			
Knowledge	Knowledge about screening procedures	I need a clear outline of the trial (13)	"I need a clear eligibility criteria and trial information to properly screen for this trial"- Participant 4
Goals	Concern for patient	I am motivated to screen for this trial because it is best for patients (5)	"If we can participate in giving a therapeutic option to those families, that is the main goal."- Participant 1
Intention	Intent to participate	I intend on participating in the trial (11)	"You know if what we're talking about is just full on SPB deficiency, you know again, we as a group would discuss it before you know moving forward and becoming a site. I don't imagine that being an issue"- Participant 9
Key theme 3: Enabling Resources			
Environmental context and resources	Access to funding	Funding is important to keep the study open and moving forward (12)	"There will be expenses that are in addition to normal standard of care, Also, if there will be additional blood testing. A lung biopsy. Anything like that. Again, that is not standard of care that that in the US were really required to separate out those expenses and the study does need to absorb"-Participant 9
	Rarity of the disease plays a factor with screening	Referral sites would have the most cases (6)	"I think if you target it to the transplant centers, I think that's going to be your highest deal, because honestly, like the average neonatologist is going to see maybe one in their career. You know, I think trying to limit the trial to a handful of transplant centers is really your best bet."-Participant 5
	The need for support and tools	Access to a genetic test that can give the results within days not weeks (12)	"Whole genome sequencing can give you the results within 18 hours, so part of the question is if you've got SPB deficiency, you know is there a faster test to at least get you into the ballpark. Because I do worry if it's going to take you know 2 ½ weeks to get your answer back the disease will be too far progressed" - Participant 3
	The physical set-up of the unit might not be ideal for participant recruitment	Site practice is different (2)	"In Europe we are probably a little less aggressive in some diseases that we think the outcome or quality of life is going to be really poor. We choose not to do certain therapies and accepting that the baby is not

			viable than go for an aggressive therapy" -Participant 14
Beliefs about consequences	Perceived disadvantages	Submitting ethics application (12)	"Anytime you're talking about human trials and babies, and especially if you're going to be messing with the genetics of the baby, the Research Ethics Board will scrutinize this protocol, with a fine-tooth comb."- Participant 7
Key theme 4: Recruiting procedures are part of their role but colleagues may have influence of trial participation			
Social/ Professional Role and Identity	Perception of screening role	It is our role to screen patients (10)	"We don't have another clinical research team; I would strongly recommend the physicians to do it."- Participant 10
		Screening is not part of our role (4)	"As a caregiver, we don't get consents because it may be sort of bias" – Participant 6
		For this trial it is my role to screen (10)	"Most parents would probably want to speak with the physician about it given the complexity of the disease."- Participant 11
Social Influence	Support from colleagues	Opinions of other colleagues' matter before approaching patients (10)	"I would consult with genetics and respirology. Surgeons potentially if there will be a transplant. and uh, and the new methodology. To see what the likelihood that the child's going to be eligible. We need to be all connected." -Participant 10

[a] Numbers in brackets indicate how many participants endorsed a specific belief statement

Key theme 1: Physicians have cautious hope about the trial (domains: Beliefs about Consequences, Knowledge)

Physicians were hopeful about the planned gene therapy trial, as many (n=15) believed that it would benefit babies diagnosed with SP-B deficiency, since there is a significant lack of treatment in this field (domain: Beliefs about Consequences). However, some (n=8) were concerned about the risks and the safety of the vector product since gene therapy is relatively fresh (domain: Beliefs about Consequences). One physician, although interested to participate in the trial, was concerned about the expected outcomes and if the therapy would result in requiring additional mechanical ventilation, causing more harm to the baby. Few(n=3) stated they require additional information about the expected outcomes after administration, the possible adverse events and how to manage them, followed by production and storage of the vector (domain: Knowledge).

> "I think that's the only treatment option left for these children. Because SP-B occurs so fast, and the accumulation of the cell is disastrous in the alveoli there is no other chance than performing gene therapy."- Participant 1

Key theme 2: Physicians feel capable to screen but require clear study procedures and outcomes (domains: Knowledge, Goals, Beliefs about Consequences, Intention)

Thirteen physicians mentioned having a clear study design, strong inclusion/ exclusion criterion, and quality feasibility of recruitment are all important factors to consider if the physicians will be

able to screen eligible patients (domain: Knowledge). Although this will add to their workload physicians (n=5) reported motivation to screen for this trial would positively aid with patient outcomes (domain: Goals). Given the rarity of the disease and the unique diagnosis, 11 physicians said they would be willing to participate and screen for this trial (domain: Intention).

> "You know if what we're talking about is just full on SPB deficiency, you know again, we as a group would discuss it before you know moving forward and becoming a site. I don't imagine that being an issue"- Participant 9 (Domain: Intention)

Key theme 3: Enabling resources (domain: Beliefs about Consequence, Environmental Context and Resources)

Several physicians (n=12) noted funding may be an issue to cover costs for genetic testing, blood tests, biopsies, and a series of regulatory ethics applications (domain: Environmental Context and Resources). Different countries have additional costs for care, which would normally be standard practice in Canada (domain: Environmental Context and Resources). One physician stated that funds will be required to cover additional costs in the intensive care unit. Due to the rarity of the SP-B disease and the small sample size of affected babies, many physicians (n=6) noted that rather than placing the focal point of the study at multiple hospital centers lacking SP-B affected babies, to focus on hospitals that frequently admit babies with rare genetic diseases as these hospitals will have a higher probability for potential participants (domain: Environmental Context and Resources).

> "There are expenses that are in addition to normal standard of care. If there will be additional blood testing, a lung biopsy, anything like that. Again, that is not standard of care. In the US we're really required to separate out those expenses and the study does need to absorb it." Participant 9 (domain: Environmental Context and Resources)

A few physicians mentioned the tedious ethical work that needs to be completed prior to trial launch (n=12) (domain: Beliefs about Consequence). Since this is an early phase gene therapy trial, the approval of the study can take several months, which can hinder trial participation of physicians. One physician also noted that, due to the rarity of the disease, it may take several months and/or year(s) to obtain a participant. A recommendation was received; having study refresher materials (short video describing the trial) that summarizes the concepts of the study can keep the study team up to date during the study. Providing a more efficient genetic diagnostic tool was also a concern voiced out (n=12) (domain: Environmental Context and Resources). Having a test that can give results within 72 hours may be beneficial to the study team and the participant. One physician noted performing prenatal genetic testing on parents with the SP-B gene may be beneficial to detect the gene early on prior to birth. Two physicians also indicated their center chooses palliative care over other treatment options if the outcome negatively impacted the quality of life (domain: Environmental Context and Resources).

> "Anytime you're talking about human trials and babies, and especially if you're going to be messing with the genetics of the baby, the Research Ethics Board will scrutinize this protocol, with a fine-tooth comb."- Participant 7 (domain: Beliefs about Consequence)

> "Whole genome sequencing can give you the results within 18 hours, so part of the question is if you've got SPB deficiency, you know is there a faster test to at least get you into the ballpark. Because I do worry if it's going to take you know 2 ½ weeks to get your answer back the disease will be too far progressed" -Participant 3 (domain: Environmental Context and Resources)

> "In Europe we are probably a little less aggressive in some diseases that we think the outcome or quality of life is going to be really poor. We choose not to do certain therapies and accepting that the baby is not viable than go for an aggressive therapy" - Participant 14 (Domain: Environment Context and Resources)

Key theme 4: Recruiting procedures are part of their role but colleagues may have influence of trial participation (domains: Social/Professional Role and Identity, and Social Influence)

Most physicians agreed that screening is part of their professional role (n=10), while four thought it was a conflict of interest to recruit participant into research, regardless of them being investigators. When describing the recruitment process, many indicated their role varied, from identifying to consenting patients. Some said the usual practice at their site is that the screening and consenting of patients is the role of the research assistant, and if the parent would like to discuss the trial with the site investigator, they would assist. However, since this is an extremely rare disease and gene therapy is new, most (n=10) felt it would be appropriate for them to approach parents, as they can discuss in detail the technicalities of the trial, including the administration of the vector and expected outcomes regarding lung transplantation (since this therapy is a bridge for transplantation). Before approaching a participant, many (n=10) voiced that the opinion of other colleagues is important to ensure if the participant is a right fit (domain: Social Influence). They described that having the genetics, respirology and transplant teams on the same page is essential for proper coordination of trial procedures.

> "Most parents would probably want to speak with the physician about it given the complexity of the disease."- Participant 11

Discussion

Gene therapy research can be very complicated and resource intensive, thus prior to trial launch, is imperative to understand the feasibility of such research. In this study, we identified barriers and enablers to screening eligible patients with physicians across different continents for an AAV gene therapy trial. The purpose of the study is to understand what support physicians require to participate for this trial. After interviewing, many physicians reported being keen to participate in this trial and screen eligible patients. The physicians were highly motivated to screen and wished to know more about the efficacy and toxicity of the gene therapy. Physicians voiced having a clear eligibility criterion; a cohesive study document including all details of the gene therapy product, trial, and expected outcomes. One physician spoke about different site practices within their institution, mentioning that the patients with incurable diseases should not succumb to experimental treatments and suffer. An unanticipated, but important issue raised, was the timing of identifying an eligible patient through genetic testing, as different institutions have limited resources to perform an adequate genetic test. Several spoke about the variability of the screening

roles, and that the screening of babies will depend on the opinion of other colleagues and their available resources.

Very few papers have assessed barriers and enablers to trial participation in early phase regenerative medical clinical research from the perspective of physicians. Rees and colleagues completed a cross sectional analysis, examining noncompletion of rare disease studies [5]. Patient accrual was the major factor for study discontinuation within 30.2% of trials (199 trials out 659)[5]. The most common reason for discontinuation were insufficient patient accrual, informative termination (data on efficacy and safety) and lack of academic funding[5]. We saw identical results with our study. By taking a comprehensive approach, we have specifically identified potential barriers physicians may face in pediatric clinical trials.

A main concern that the physicians identified was the potential risk of the AAV gene therapy product and uncertainties associated with gene therapy in babies. Our findings were consistent with a previous systematic review that cited uncertainty of a clinical trial being a barrier[6]. Though it is the second most used vector, one issue that comes up in other clinical trials is the possibility of provoking a severe immune and inflammatory response[10]. Two other studies, focusing on barriers with early phase stem cell trial and Chimeric antigen receptor (CAR) T-cell therapy, found similar results with physicians concerned with the safety aspect of the trial, that may impede their ability to screen patients[25,26]. To overcome this barrier, providing articles on the lack of other treatment options (lung transplantation)[27], treatment efficacy in animal models[4], and feasibility of AAV in other clinical trials might help address physician concerns [9]. Providing these resources may increase physicians' comfort and confidence to screen. Recruiter training can also be an option to help address this barrier[28]. Most training programs are focused on communication strategies, explaining key concepts of the trial (randomization) and exploring patient preference[28]. The training program should also include results on the toxicity and safety of the AAV product, as well as potential patient outcomes, with and without the experimental treatment.

The highly motivated physicians in this study identified barriers to recruitment as including the need for additional resources and lack of patients due to the rarity of the disease. This was also consistent in the systematic review, which stated lack of resources impacted the ability to participate in clinical trials[14]. Essential elements in the success of the trial include but are not limited to: costs involved in participating in trials, submitting ethics applications, and having an infrastructure with appropriate support from formal and informal bodies. The commercially available genetic testing is a major concern for participant enrolment as the interpretation of results may not be straightforward, the turn-around time can take up to three weeks, and it is not cost efficient[29]. This is a concern as the baby's health deteriorates rapidly and they may not be eligible to participate. Collaborating with a genome institute can be an option, as they can provide a whole genome sequencing test, which may help with a quicker diagnosis as genes of interest can be extracted from the analysis[29].

Implementing the trial at referral sites, rather than multiple research hospitals, can have a higher probability to reach our recruitment numbers for the gene therapy trial. Instead of focusing on multiple sites to reach the sample size for the future gene therapy trial, we should focus on main referral centers that specialize in treating rare diseases and allocate resources and sufficient funds to those sites, hoping to see SP-B patients. A way to optimize trial recruitment at these referral

sites is to bring awareness of this study to fellow physicians, thus increasing referrals of suspected patients of SP-B. This can be done by presenting about the trial's aim to treat SP-B patients at conferences, grand rounds, and pediatric networks. Another study for another rare disease, Spinal Muscular Atrophy (SMA), has established trial sites with the highest level of clinical expertise. Due to the high unmet medical need for children with SMA, the sponsor of the trial was willing to support travel to families when there were not study sites nearby. This strategy can be used within the AAV trial given the available funding[34].

Site screening practices differ from center to center. Some expect research coordinators to approach families, other sites have the physicians' approach. In order to prevent variability with consenting patients, it is important to have an agreement of screening practices, with clarification of the recruitment roles. Most of the physicians agree, that for this trial, they should be involved in the consent process. They can speak to parents about the gene therapy treatment and answer any technical questions that the others may not have answers for. Parents have also stated that they would like to hear about the trial from the physician, who knows their baby's health, and can help them understand if participating in the trial is a right fit [7]. Parents are more inclined to hear about a trial from a physician, as they see them as trustworthy and knowledgeable individuals[30–32]. However, many physicians are busy, as they have other commitments and to respect their time, the use of lay navigators may be beneficial to optimize trial recrutiment[14]. There needs to be a balance of what parents want and what is reasonable for the physicians' workload. Faytre *et al*., showed that participants approached by individuals that are non-physicians and trained to provide information on the trial were more inclined to participate in the trial[14]. This strategy can help alleviate physicians' workload and still provide all the informational needs to participants. Bringing awareness of the trial to other clinical professionals, especially with the attending physicians, is important so they can discuss the trial with their patients. Clinicians buy-in is important, as many physicians want to consult with the rest of the clinical team before approaching the patient[13]. Advocating the importance of the research and engaging everyone in the unit, including nurses, attending physicians, and others will facilitate recruitment. However, the principal message should come from the research physician[13].

Strengths and limitations

One limitation to this study was focusing strictly on neonatologists and pulmonologists. They are the most relevant healthcare provider identified by the trial team. Although they provided essential information, many stated that other research staff involved with the screening and consenting of patients are of equal importance. When expanding to later phases of the study, future research should assess the unanticipated barriers and enablers, by other staff involved in the recruitment process. Another limitation is the low response rate in this interview study from potential trial participants. This may be due to physician's lack of availability to participate in the interviews and due to prominent language barriers since the interviews were only conducted in English. The strength of this study lies in the use of the TDF to identify factors that may impact physicians screening and recruiting behavior. The TDF gave a comprehensive assessment of the potential barriers and enablers to screening and recruiting to an early phase AAV gene therapy trial. This enables comparison to other similarly conducted studies, which we can leverage across trials and by linking the research findings to the therapy, allows us to generate evidence-based strategies that other trialists can use.

Conclusion

Translating clinical research into clinical practice is a challenge, as there are barriers towards trial recruitment. It is essential for clinical trials to be initiated, given the critical need for therapeutic development for rare disease and the small patient populations available to generate robust clinical evidence. Only a limited number of pediatric patients with this disease are available at a given time for enrollment. Collaborations with neonatologists and pulmonologists is a priority in the development and execution of this trial, which will help attain trial enrolment goals and enable a more patient-centric approach. Due to the scarcity of treatment options and low quality of evidence for this rare disease, it is imperative to give these babies a chance at survival. As the needs and demands for pediatric research increase, researchers need to find strategies to overcome unexpected barriers.

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Appendix A: Interview Guide for Neonatologists

Introduction:

- Thank you for agreeing to speak with me today about your thoughts and views about genetic therapy, which may be useful to treat surfactant protein deficiency.
- Discussion should take approximately 30-40 minutes
- Audio-recorded to ensure that key points documented
- Any identifying info (e.g., name or names of others) used during our discussion will be removed
- If you want to end our discussion before I ask all questions or if you want to withdraw from the study, you are free to do so.
- I am interested in your views about gene therapy in particular adeno-associated virus (AAV)-mediated gene targeting technology, thus we can appropriately plan our future research in this area

Demographic and background questions

(Record whether male or female)

What is your current age?

How many years have you been a practicing neonatologist?

Are you currently employed full-time?

- If no, what is your current employment situation? E.g., on leave, working part time
- If working part-time what proportion of your work time is dedicated to direct patient care?

Have you ever encountered in your current clinical practice of a patient with inherited surfactant protein deficiency?

In your center, do the physicians screen patients for trials? (If answer is no: Do they contribute to identify potential patients for trials and liaise with research team?)

25. Can you tell me about your past experience screening any patients for any clinical trial?
    - PROMPT: Have you screened patients for trials in the past? (DOMAIN: SKILLS)
    - PROMPT: (If yes) How did that go?

26. Have you ever received training to screen patients for a clinical trial as a clinician? If so, what was most helpful about the training? (DOMAIN: SKILLS)
    - PROMPT: If not, what training do you think would be most helpful for yourself or others involved?

27. What do you know about gene therapy in general, and for inherited surfactant protein deficiency in particular? (DOMAIN: KNOWLEDGE)
    - PROMPT: What information would you need to feel comfortable talking to a family about a gene therapy trial for surfactant deficiency, as part of screening for trial participation? (DOMAIN: KNOWLEDGE)
    - PROMPT: Have any parents ever asked you about gene therapy/ other treatment options? What was discussed?

28. In your opinion, is screening for patients with surfactant protein deficiency for a gene therapy trial a priority for you? (DOMAIN: GOAL)

Background information about gene therapy shared with the physician if needed

We are planning to run a first in human gene therapy trial for patients with surfactant protein deficiency. But prior to conducting that trial, we want to make sure to build in your views about administrating gene therapy to infants and recruiting for a potential trial in the future.

In relation to that and for the rest of our discussion, I would like you to think of the following specific activity:

Please imagine that you <u>are personally identifying newborns with suspected inherited anomaly with surfactant metabolism,</u> for potential participation in a clinical trial of gene therapy. You are doing this activity for the trial research assistants, i.e., not to fully enroll the patients but to scree them for eligibility. For short, I will call this "identifying potential patients" for the remainder of our discussion but by that I mean this more specific activity.

General first question:

29. Thinking about your own experiences, what might be some reasons that you would not be able to identify potential patients (i.e., newborns with a suspected inherited anomaly of surfactant metabolism) for a clinical trial? (DOMAIN: DEPENDS ON RESPONSE)
    a. PROMPT: Do you see any unforeseen obstacles?

30. Imagine yourself identifying a potential patient. Can you briefly walk me through the steps that you would use to go about that? (DOMAIN: KNOWLEDGE)

31. What are the specific techniques or skills that you need to identify potential patients for enrollment for this trial? (DOMAIN: SKILLS)

32. How do you see identifying potential patients for this trial in relation to your role as a clinician? (DOMAIN: SOCIAL PROFESSIONAL/ROLE AND ID)
    a. PROMPT: Do you see this as something that is a part of your current role?
    - PROMPT: Do you think it should be part of your role? Whose role should it be? Who else should be involved?
    - PROMPT: What would be your responsibilities in this position?

33. Do you think that a physician should be involved in the consenting process for a new intervention, like a gene therapy trial? (DOMAIN: SOCIAL PROFESSIONAL/ROLE AND ID)

34. You mentioned earlier a few reasons that might stop you from being able to screen patients for a clinical trial. How confident are you that you could identify suspected babies on your unit for a potential gene therapy trial if one were to take place in the next 2 years? (DOMAIN: BELIEFS ABOUT CAPABILITIES)
    a. PROMPT: What would make you feel more confident?
    b. PROMPT: What would make you feel less confident?

35. What are some of the benefits that you see of identifying potential patients for a gene therapy trial for inherited surfactant protein deficiency? (DOMAIN: BELIEFS ABOUT CONSEQUENCES)

a. PROMPT: For you, for patients enrolled in the trial (symptoms/ treatment?), for future patients, for their parents/families, for anyone else, for advancing research, personal benefit

36. What patient outcomes do you think a new gene therapy could target for improvement? (DOMAIN: GOALS)
    a. PROMPT: What do you think your patients will achieve if they receive this gene therapy treatment? (DOMAIN: BELIEFS ABOUT CONSEQUENCES)

37. What are some of the disadvantages that you see of identifying potential patients for a gene therapy trial for inherited surfactant protein deficiency? (DOMAIN: BELIEFS ABOUT CONSEQUENCES)
    a. PROMPT: For you, for your patients, for anyone else. Risks/side effects?

Offer to describe possible known side effect and negative consequences. Once described, ask: do the benefits outweigh the potential harms?

38. Do you expect that identifying potential patients for this trial will result in more good things or bad things? PROMPT: In what way? (DOMAIN: OPTIMISM)

39. Based on the information you have right now, would you be interested in participating to identify potential patients as part of a gene therapy trial for inherited surfactant protein deficiency if one is available in the next year? (DOMAIN: INTENTION)
    PROMPT: Why/Why not?
    PROMPT: How motivated are you to identify potential patients if the trial's goal was to test the safety of the gene therapy, but not to test if it improved your patients' health? (DOMAIN: INTENTION)

40. To what extent do you think competing priorities related to patient care would impact your ability to identify patients for this trial? (DOMAIN: GOAL)
    a. PROMPT: Might something be more urgent? What?
    b. PROMPT: How do you think these priorities will impact your ability to identify patients for the trial?
    c. PROMPT: Will it be easier to screen (identify patients) when you are on clinical duty or when you are off service? (DOMAIN: ENVIRONMENTAL CONTEXT AND RESOURCES)

41. What would motivate you to regularly and routinely identify potential patients for gene therapy trial for inherited surfactant protein deficiency? (DOMAIN: REINFORCEMENT)
    a. PROMPT: Any social/ personal benefit? Recruitment target?

42. Do you think it is likely that you might sometimes forget to identify potential patients for this trial? When would you most likely forget? What might help? (DOMAIN: MEMORY, ATTENTION, DECISION PROCESSES)
    a. PROMPT: reminders?

43. What are some strategies you would use to stay on top of identifying potential babies? (DOMAIN: BEHAVIORAL REGULATION)

PROMPT: What can you do personally to help stay on top of identifying potential patients? (Not the clinic/anyone else)
PROMPT: Are there any strategies you have used in the past that has helped you stay on top of identifying potential patients that might help other neonatologists?

44. What resources do you need to be made available to you to identify potential patients for this trial? What resources do you already have? (ENVIRONMENTAL CONTEXT AND RESOURCES)
    a. PROMPT: institutional support, financial support, research nurses, trained research assistant
    b. PROMPT: What tools might help?

    Is there anything about the physical setup of the unit/ward itself that (could) influence whether or not you identify potential patients?
    - Prompt: space, time, place to do this

45. Are you comfortable with the process of requesting a genetic test for your patients? Do you see any barriers to requesting a genetic test if required as part of screening for this potential gene therapy trial? (DOMAIN: SOCIAL PROFESSIONAL/ROLE AND ID)

46. Who else's views are important to you when deciding to identify babies for this trial, and when you screen/identify them? (DOMAIN: SOCIAL INFLUENCES)
    a. PROMPT: patient's family, other physicians, colleagues, results of other phase 1 trial about gene therapy and surfactant deficiency

47. How would identifying potential patients add any level of stress to your current workload? (DOMAIN: EMOTION)
    PROMPT: How would that stress influence identifying potential patients for this trial? (ie. Reluctant, not want to get involved, etc.)

48. Do you see anything else as being a barrier to identifying potential patients for this clinical trial?

49. Based on what we have discussed, what would you say is the most important factor influencing you personally identifying potentially eligible babies on your unit?

50. What would you say is the most important factor to provide ongoing care in a gene therapy trial for inherited surfactant protein deficiency?

Any final thoughts?
Thanks so much for your time!

Appendix B: Summary of belief statements and sample quotes from participants assigned to domains identified as relevant

Domain	Subtheme	Belief statement	Frequency (out of 18) (n=%)	Sample quote
Knowledge	Knowledge of gene therapy	I am aware of clinical trials using AAV vector in the pediatric population	9 (50)	"I'm very aware that gene therapy is a field as a strategy, but not for this particular condition. I think about cystic fibrosis. The problem is in the lung you must reach it. You know with gene therapy you have to reach the lung, and this is what is difficult, and this is what is the problem in CF because you need to give some vectors that can reach the cell and When you talk of CF you talk of bronchi that are completely stuck so it's really difficult and with a very reactive."-Physician 7
		I am unaware of the use of AAV	2 (11)	"Do not know much about it but if it can help with other than going for lung transplantation, I would be keen on to going with it"- Participant 8
	Knowledge about screening procedures	I know the steps that would be taken to screen patients for this trial	13 (72)	"The first step is patient identification. Pre or late preterm whose respiratory condition lung disease doesn't evolve as we think it should get genetic testing for. Once confirmed and eligible for the study we will approach parents"- Physician 13
		I need a clear eligibility criteria and trial information to properly screen for this trial	13 (72)	"The protocol needs to be clear with a clear eligibility criterion in order to screen for these patients. Also, the study procedures, if a child is on ECMO do we take them off… things like that."- Physician 9
		I would need knowledge of the logistics of the AAV production and storage	3 (17)	"So how and where do we get the study drug from? How does it get transported? Are there some laboratories in Germany or somewhere else? Who are allowed to produce this? Or do we have to wait from the laboratory from Canada? So these are things I think are logistic."-Participant 18
	Existing knowledge about AAV therapy	I would like to know more about toxicity, adverse events and expected outcomes	9 (50)	"I would need to know how safe it is, how invasive. What are the preliminary data? How? What's the likelihood that it could work?"- Participant 5
Environmental context and resources	The physical set-up of the unit might not be ideal for participant recruitment	My institution may not be able to support a clinical trial without additional support	5 (28)	"We don't have our NICU department in this House, basically because this is a pure children hospital. We don't have a delivery room and so we have a regular Intensive care unit and the NICU would be in a separate building about 1 kilometer down the road"- Participant 1
		My institution has the resources and structure to support the trial	10 (55)	"We have all kinds of study coordinators and clinical research support people. And you know what they do every day as they go into the NICU. You look at all our studies. We have about 10. We've done Phase 1 studies pretty smoothly"- Participant 3

		Site practice is different	2 (11)	"In Europe we are probably a little less aggressive in some diseases that we think the outcome or quality of life is going to be really poor. We choose not to do certain therapies and accepting that the baby is not viable than go for an aggressive therapy" - Participant 14
	Rarity of the disease plays a factor with screening	Referral sites would have the most cases	6 (33)	"I think if you target it to the transplant centers, I think that's going to be your highest deal, because honestly, like the average neonatologist is going to see maybe one in their career. You know, I think trying to limit the trial to a handful of transplant centers is really your best bet."-Participant 5
		The time and effort to not recruit even 1 patient is a concern	11 (61)	"And even at my center, even if I'm still here would the major discussion is if we can afford the time and energy. If this is going for 4 years and there is still not a patient that can demotivate a lot of people"- Participant 2
	The need for support and tools	Education for support staff	4 (22)	"Since the disease is so rare, documents or tools will be helpful as a refresher for the nurses and staff. There's no point in doing a bunch of education and then three years later you get your patient. So maybe having a short video about the study, if you get a patient, here's what you watch, and this is what I would also encourage your team to do." Participant 7
		Documentation and guidance to submit to ethics will be helpful	15 (83)	"All the biggest work is in the beginning is, as you said, the making of all the paperwork for the institutional review board, so that's something that we definitely need support from you."-Participant 5
		Access to a genetic test that can give the results within days not weeks	12 (67)	"Whole genome sequencing can give you the results within 18 hours, so part of the question is if you've got SPB deficiency, you know is there a faster test to at least get you into the ballpark. Because I do worry if it's going to take you know 2 ½ weeks to get your answer back the disease will be too far progressed" -Participant 3
	Access to funding	Funding is important to keep the study open and moving forward	12 (67)	"There will be expenses that are in addition to normal standard of care, Also, if there will be additional blood testing. A lung biopsy. Anything like that. Again, that is not standard of care that that in the US were really required to separate out those expenses and the study does need to absorb"- Participant 9
		Study staff	3 (17)	"It's probably mostly financial. To get people and to pay them too. And to help out with the study start up and to open the center up as an active site" - Participant 3
	Physician's workload/ time	Even if I am busy, I will be available to screen/ consent	8 (44)	"For this study, it will not require a lot of effort like other that we participate in. So this isn't one that I would require a lot of effort for me to be checking in. Since this is such a rare disease, if you get 1 the

				whole unit will be aware and on board"-Participant 7
		It does not matter if I am on service or off to screen/ consent	15 (83)	"Our unit works together, so if they see a SP-B patient they will notify the team if I am not there"- participant 10
Beliefs about consequences	Perceived disadvantages	Submitting ethics application	12 (67)	"Anytime you're talking about human trials and babies, and especially if you're going to be messing with the genetics of the baby, the Research Ethics Board will scrutinize this protocol, with a fine-tooth comb."- Participant 7
		Unknown safety and efficacy	8 (44)	"I think there would be potentially concern of causing an immunological sort of response. Then would the babies then require more oxygen or respiratory support? I think that would be the biggest concern." – Participant 5
	Treatment benefits	The trial will benefit the patients that have no other treatment option	15 (83)	"Basically, we have no treatment. The outcome is very poor, and I would be very positive about a new treatment that might offer help. They really haven't got very much to lose. I'd be strongly in favour."- Participant 7
		Parent's will participate even it may not benefit the child	3 (17)	"I think, for phase one phase and phase two trials, it probably won't benefit the child because you are looking at safety and efficacy, but parents may be willing to participate if they think, even if it is for validation. They will try anything to save their baby."- Participant 6
	Long-term benefit	Advancing scientific research	15 (83)	"There is potential to advance care. For this rare disease there is huge potential. Since there is high morbidity and mortality rate. These are one of those rare conditions where it's hard to make advances because very few companies are going to."- Participant 11
		Help increase awareness in the community	3 (36)	"You can really increase the awareness. Not all neonatologists are aware of SP-B and it's not easy to discuss different treatment options with parents."- Participant 11
	Study design	Lack of patients	5 (28)	"I don't know why your principal investigator is so optimistic because across of all of Europe we had 10 patients. It's rare. It's great that you have this optimism still going."- Participant 2
		Site practice is different	2 (11)	"In Europe we are probably a little less aggressive in some diseases that we think the outcome or quality of life is going to be really poor. We choose not to do certain therapies and accepting that the baby is not viable than go for an aggressive therapy" - Participant 14
Beliefs about capabilities	Confident	I feel confident in my ability to screen/ recruit patients for this study	6 (33)	"I am confident. I'm pretty sure that that we would find. Almost all the children that potentially have this disease are ventilated for a period and if that is the case, we for sure do a genetic testing. We will find them."- Participant 1

	Somewhat confident	I am confident to screen for this trial if I know more information about this study	1 (5)	"I am confident to screen but I would need information about the study vector and what were the effects for those babies once they get the transplant"- Participant 5
	Not confident	I am confident to screen/ recruit patients but not confident to find any patients given the rarity of the disease	3 (17)	"I'm confident with screening because it is a rare disease we will know if we have an eligible patient but I'm just saying I'm not confident that we'll find any." -Participant 18
Goals	Priority	Screening is my top priority	6 (33)	"For this rare disease, screening would not be an issue. It will be on our radar if a baby has suspected SP-B. So it will be my top priority"- Participant 6
		I have other competing priorities	4 (22)	"No, it's definitely interesting. It's not on the top of my priority because it's a very rare disease, but if any child you can offer good help with and a good outcome. But as I say, if the outcome is getting them to lung transplantation, I'm not sure."- Participant 14
	Concern for patient	I am motivated to screen for this trial because it is best for patients	5 (28)	"If we can participate in giving a therapeutic option to those families, that is the main goal."- Participant 1
	Advancing science	Screening patients is important to contribute to this field	5 (28)	"Help to get the diagnosis early and intervening before there's permanent injury or potentially death. I think there's going to be really important to the field."- Participant 3
Intention	Intent to participate	I intend on participating in the trial	11 (61)	"You know if what we're talking about is just full on SPB deficiency, you know again, we as a group would discuss it before you know moving forward and becoming a site. I don't imagine that being an issue"- Participant 9
		Support Bernard Thébaud and his research	2 (11)	"The only reason I'd be involved is because of Bernard and our relationship. Obviously, we want to help the kids, but I know Bernard very well."- Participant 3
	Intent to not to participate	I do not intent to screen/ participate in the trial	2 (11)	"I don't think we would be participating in this trial. We would be referring most of these patients to Sick Kids"- Participant 11
	Conditional intent	We might intend of participating in this trial	3 (17)	"We can definitely talk about it, but I think I would need a little bit more experience and data on the trial"- Participant 14
Skills	Request of additional tests	I have requested genetic testing before	12 (67)	"I think if you say that what we need is basically the genetic testing, and this is what we do and what we have access to and we give them out regularly"- Participant 3
	Screening is part of the job	We screen daily	10 (55)	"The cases are so rare that we would know if there were a baby with an identified mutation. We will call the research coordinator or the site to let them know." Participant 10

	Formal training	We have the formal training required to perform clinical trials	3 (17)	"In my center we all need GCP training and have to refresh them every now or then when there's an update otherwise, you're not allowed to participate in trials" Participant 2
Social Influence	Support from colleagues	Opinions of other colleagues' matter before approaching patients	10 (55)	"I would consult with genetics and respirology. Surgeons potentially, if there will be a transplant. and uh, and the new methodology. To see what the likelihood that the child's going to be eligible. We need to be all connected." -Participant 10
		Support from other neonatologists	6 (33)	"A team of neonatologists, they need to inform us of course about those children and make us aware of the case. They see a child in the unit and then we discuss the case together. I would say we would be dependent on the on the neonatology team"- Participant 18
Emotion	Emotion is neither a barrier nor enabler	No additional stress to workload	8 (44)	"To me no. you know I think it's really exciting to think about potential therapy for this."-Participant 5
		There will be additional stress to workload	10 (56)	"Of course, it will ass stress, everything does. None of us have time, but it's if it's an important study and it's going to take a baby who would die otherwise. That that's what we do. Why we do what we do right?"- Participant 3
Memory, attention and decision process making	Treatment option	To screen patients for this trial, I would need to know response rate from other parents	1 (5)	"Personally, if I had a patient with surfactant protein B deficiency, whose family was fully on board for transplant, I would feel better knowing that other babies with the same disorder whose parents did not do transplant received the AAV vector first and get a sense of what their responses were"- Participant 5
Optimism	Optimism	I would expect more good things than bad	6 (33)	"I hope so. We are at this phase of research because it's based on information already that provides us with hope"- Participant #5
Reinforcement	Previous clinical trial experience	I have experience with clinical trials	14 (78)	"Yes, we do a lot of clinical trials. Generally, they are very good. So, we run a lot of early phase clinical trials in children and have a great experience with it."- Participant 17
	Case of SP-B	I have seen very few patients with SP-B	9 (50)	"Yeah, I think I have two cases of surfactant B deficiency, so in my 40 years I have two cases of surfactant B deficiency."- Participant 6
Social/ Professional Role and Identity	Perception of screening role	It is our role to screen patients	10 (56)	"We don't have another clinical research team; I would strongly recommend the physicians to do it." – Participant 10
		For this trial it is my role to screen	10 (56)	"Most parents would probably want to speak with the physician about it given the complexity of the disease."- Participant 11
		Screening is not part of our role	4 (22)	"As a caregiver, we don't get consents because it may be sort of bias" – Participant 6
	Variability of screening roles	Screening is done by the research team with the assistant from the physician	4 (22)	"Screening should be done by both. Because a research assistant associate will not be able to answer questions derived from the testing. So, it should be both". – Participant 13

Appendix C: Subthemes and Beliefs Statements

Most Relevant Domains

The most relevant domains were identified based on the criteria outlined by Atkins et al. (2017). Relevant domains were chosen based on the frequency with which beliefs and themes appeared in each domain, the presence of conflicting beliefs, and perceived relevance to the target behaviour.

Domain	**Number of participants represented**	**Total number of instances coded to domain**
Reinforcement	16	53
Nature of behaviour	0	0
Optimism	6	18
Skills	15	31
Behaviour regulation	0	0
Memory, attention and decision making	1	1
Beliefs about capabilities	8	28
Emotion	18	21
Social influence	15	37
Intention	16	23
Goals	12	31
Social and professional role and identity	12	23
Beliefs about consequences	17	88
Knowledge	13	71
Environmental context and resources	15	137

Knowledge

***N* = 13**

Knowledge of Trials

Most physicians (*n* = 9) were aware gene therapy clinical trials, and many mentioned the use to treat cystic fibrosis. Physicians expressed knowledge regarding the difficulties to conduct such trials and having the stability of the vectors.

> R: "I'm very aware that gene therapy is a field as a strategy, but not for this condition. I think about cystic fibrosis. The problem is in the lung you must reach it. You know with gene therapy you have to reach the lung, and this is what is difficult, and this is what is the problem in CF because you need to give some vectors that can reach the cell and when you talk of CF you talk of bronchi that are completely stuck so it's really difficult and with a very reactive."
> *Physician #7*

Some physicians (n=2) indicated not knowing a lot about the use of AVV as it is a novel treatment option. Despite their perceived lack of knowledge, they were still optimistic about the trial

> R: "Do not know much about it but if it can help with other than going for lung transplantation, I would be keen on to going with it"
> *Physician #* 8

Screening Procedures

Most physicians (*n* = 13) indicated knowing about screening procedures and were readily able to describe the process their unit undertakes when identifying, screening and enrolling patients into a clinical trial. Physicians often discussed additional behaviours in their description of screening procedures including reviewing patient charts, identifying patients, obtaining pre-screening consent, ordering tests, assessing for eligibility, coordinating with study staff, educating patients and caregivers and obtaining informed consent for the actual trial.

> R: "The first step is patient identification. Pre or late preterm whose respiratory condition lung disease doesn't evolve as we think it should get genetic testing for. Once confirmed and eligible for the study we will approach parents"- Physician 13

This suggests that screening involves several actions and behaviours that may involve distinct barriers and enablers.

Physicians (*n* = 13) indicated that it was important for them to have clear eligibility criteria and trial information.

> R: The protocol needs to be clear with a clear eligibility criterion in order to screen for these patients. Also, the study procedures, if a child is on ECMO do we take them off… things like that.
> *Physician # 9*

Three physicians mentioned required information about the logistical aspects of the trial and treatment as that plays an important role when discussing the trial with their clinical staff.

> So how and where do we get the study drug from? How does it get transported? Are there some laboratories in Germany or somewhere else? Who are allowed to produce this? Or do we have to wait from the laboratory from Canada? So these are things I think are logistic.
> *Physician # 18*

Existing knowledge about AAV therapy

Physicians (*n*=9) identified having a clear idea about how safe and invasive the AAV vector is very important. Especially, the expected outcomes, thus when telling parents about the trial, there are clear expectation.

> R: I would need to know how safe it is, how invasive. What are the preliminary data? How? What's the likelihood that it could work?
> *Physician # 5*

Environmental Context and Resources

***N* = 15**

Institutional Capacity

Several physicians (*n* = 5) discussed how institutional capacity impacted their ability to screen/ consent patients. For some pulmonologists they mentioned that they work with other hospitals that have a NICU center, they perceived that they would need patients to be referred to their hospital in order to participate.

> R: We don't have our NIU department in this House, basically because this is a pure children hospital. We don't have a delivery room and so we have a regular Intensive care unit and the NICU would be in a separate building about 1 kilometer down the road-
> *Physician #1*

Other physicians (*n*=10) said that they are well equipped to participate in the trial, and they have the support from the institution and very familiar with Phase 1 trials.

> R: We have all kinds of study coordinators and clinical research support people. And you know what they do every day as they go into the NICU. You look at all our studies. We have about 10. We've done Phase 1 studies smoothly
> *Physician #3*

Eleven physicians noted, however, that smaller hospitals may not have the resources to support a AAV trial due to the rarity of the disease. They suggested that smaller institutions may not even see a patient throughout the lifespan of the trial. Six physicians suggested that targeting referral centers may be a better option to meet recruitment numbers.

> R: I think if you target it to the transplant centers, I think that's going to be your highest deal, because honestly, like the average neonatologist is going to see maybe one in their career. You know, I think trying to limit the trial to a handful of transplant centers is really your best bet.

Physician #5

Additionally, two physicians suggested that their site practice with care is different. If there is child with this disease that will impact their quality of life, they tend to support palliative care, rather having the child go through intense and extensive treatment.

> R: In Europe we are probably a little less aggressive in some diseases that we think the outcome or quality of life is going to be poor. We choose not to do certain therapies and accepting that the baby is not viable than go for an aggressive therapy
> *Physician #14*

Additional support and tools

The need for education of the study was mentioned by four physicians. Training materials, regular communication were some things that the physicians required to be on top of the study. Since the disease is extremely rare, some research staff might forget the details of the trial. thus regular meetings and or videos were suggested as a refresher.

> R: Since the disease is so rare, documents or tools will be helpful as a refresher for the nurses and staff. There's no point in doing a bunch of education and then three years later you get your patient. So maybe having a short video about the study, if you get a patient, here's what you watch, and this is what I would also encourage your team to do
> *Physician #7*

One common factor was the guidance required to submit the project to the ethics committee. Many physicians (*n*=15) said they need help with the submission and have the required documents. Different countries have different regulations; thus the study team needs to be mindful of that.

> R: All the biggest work is in the beginning is, as you said, the making of all the paperwork for the institutional review board, so that's something that we need support from you.
> *Physician #3*

Moreover, access to faster genetic test was voiced out by many physicians (*n*= 12). The regur commercial testing. They indicated having a whole genome sequencing test can provide results within days rather than weeks.

> R: Whole genome sequencing can give you the results within 18 hours, so part of the question is if you've got SPB deficiency, you know is there a faster test to at least get you into the ballpark. Because I do worry if it's going to take you know 2 ½ weeks to get your answer back the disease will be too far progressed
> *Physician # 3*

Funding

A related concern voiced by 15 physicians had to do with available funding to support the trial. Twelve physicians mentioned the need to provide trial sites with funding to cover the costs of a

variety of procedures including blood and imaging tests, biopsies, trial related treatments, coordination of care with other departments, hospital beds, the costs associated administrative aspects of the trial like REB approval.

> R: There will be expenses that are in addition to normal standard of care, Also, if there will be additional blood testing. A lung biopsy. Anything like that. Again, that is not standard of care that that in the US were really required to separate out those expenses and the study does need to absorb
> *Physician #12*

Three doctors specifically mentioned the need to fund research personnel. One physician mentioned at their center they do not have a research team as the lead investigator takes on the project roles. Another physician mentioned that compensating research nurses as well as their team for their time working on the project and how will the sites get the funding, would it be per patient?

> R: There are some financial issues involved. So how do you work in the funding? Will it be by patient? You know you can't cover people's salary because you may never get a patient, since it is so rare
> *Physician #3*

Physician Time and Workload

Since this disease it extremely rare, many said that it would not be time consuming to screen/ consent patients since the symptoms are very apparent (*n*= 8). Majority have said that regardless of if they are on service or off. Everyone in their unit will be onboard and notify the physicians if there is a case.

> R: For this study, it will not require a lot of effort like other that we participate in. So, this isn't one that I would require a lot of effort for me to be checking in. Since this is such a rare disease, if you get 1 the whole unit will be aware and on board
> *Physicians #7*

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> R1: Our unit works together, so if they see a SP-B patient they will notify the team if I am not there
> *Physicians # 10*

Belief about Consequences

***N* = 17**

Perceived Benefits

Physicians identified treatment benefits as the primary positive outcome of having patients participate in a AAV gene therapy clinical trial. The majority (*n* = 15) indicated that this trial is beneficial because it offers patients with a treatment option that has no other alternative other than lung transplantation. Many (*n*= 15) voiced out that it will help advance gene therapy research in the field especially with this ultra-rare disease which is overlooked by the industry.

> R: Basically, we have no treatment. The outcome is very poor, and I would be very positive about a new treatment that might offer help. They really haven't got very much to lose. I'd be strongly in favour
> *Physician #7*

> R1: There is potential to advance care. For this rare disease there is huge potential. Since there is high morbidity and mortality rate. These are one of those rare conditions where it's hard to make advances because very few companies are going to
> *Physician #11*

As suggested by these two quotes, physicians expressed a lot of hope and excitement for the therapy. Their motivation was primarily focused on what is best for patients and specifically increasing their chances of survival.

A few physicians (n = 3) also suggested that this will bring awareness of the disease and a potential treatment option for parents. It can help physicians refer their patients to centers who are conducting this trial

> R: You can really increase the awareness. Not all neonatologists are aware of SP-B and it's not easy to discuss different treatment options with parents
> *Physician #7*

Three also noted that parent's will be inclined to participate in this trial even if it does not benefit their child. They will do anything to give their child a chance at survival.

<u>Perceived Disadvantages</u>
While physicians mentioned anticipated benefits more often than they did costs, eight physicians discussed their concerns regarding safety (n = 8), and the logistical factors including ethic submissions (n = 12)

> R: I think there would be potentially concern of causing an immunological sort of response. Then would the babies then require more oxygen or respiratory support? I think that would be the biggest concern.
> *Physician #5*

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> R: Anytime you're talking about human trials and babies, and especially if you're going to be messing with the genetics of the baby, the Research Ethics Board will scrutinize this protocol, with a fine-tooth comb. So, we need to make sure what we give has all the information so there will not no delays
> *Physician #7*

How well toxicity and side effects are managed may potentially influence a physician's screening assessment and decision regarding patient enrollment. It will be important to demonstrate to the physicians that toxicity management guidelines are evidenced-based and well-reasoned. Also, provide them support for their regulatory applications, as that is one major barrier for their trial participation. Having appropriate documents prepared for distribution will help with the submission process.

Study Design and Feasibility

Study design and feasibility was of great concern to at least seven physicians. Many suggested that given the rarity of the SP-B, finding enough eligible participants to screen for the trial will likely be a challenge. In fact, five neonatologists suggested they expect to identify very few eligible participants. Three suggested that due to lack of patients is barrier to them to participate in this trial. With the ethics submission and keeping the trial open for not even seeing one patient is a concern. One even suggested that we are being optimistic with this trial since finding these patients is extremely difficult.

> R: I can't promise that I will be successful with screening because it is so rare, and it depends on the frequency of examinations, and it depends on the kind of examinations depends on logistic things
> *Physician #18*

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> R1: I don't know why your principal investigator is so optimistic because across of all of Europe we had 10 patients. It's rare. It's great that you have this optimism still going.
> *Physician #2*

Beliefs about Capabilities

***N* = 8**

Of those who were coded into this domain, six indicated that they would be confident in screening and recruiting patients for an AAV clinical trial.

> R: I am confident. I'm pretty sure that that we would find. Almost all the children that potentially have this disease are ventilated for a period and if that is the case, we for sure do a genetic testing. We will find them.
> *Physician #1*

One physician indicated that they would feel more confident if they had more information regarding the safety and efficacy of therapy as well as the expected outcomes.

> R: I think so long as I believe that a trial has been designed well and is being conducted will and its safety of patients is paramount then I'm comfortable raising it. And if people say no that's fine, but I, I have no qualms about offering discussion about possible clinical trials.
> *Physician #12*

Only one physician indicated they did not feel confident in screening for a CAR-T trial citing doubts about the study design and feasibility.

> R: I am confident to screen but I would need information about the study vector and what were the effects for those babies once they get the transplant
> *Physician #5*

Finally, three physicians suggested they are confident with screening for patients but not confident in recruiting any patients due to rarity of the disease.

> R: I'm confident with screening because it is a rare disease we will know if we have an eligible patient but I'm just saying I'm not confident that we'll find any.
> *Physician #18*

Goals

***N* = 12**

Physicians were primarily motivated by their concern for patients. Every physician expressed a preference for screening for trials that would benefit their patients. Five participants indicated they were motivated to screen for a gene therapy trial because it offered their patients an opportunity for treatment where no other options exist.

> R: If we can participate in giving a therapeutic option to those families, that is the main goal.
> *Physician #1*

A few physicians (n = 5) were concerned with advancing the science of AAV gene therapy and indicated that screening for this clinical trial was important because it added to their knowledge base and provide better safety data.

> R: Help to get the diagnosis early and intervening before there's permanent injury or potentially death. I think there's going to be important to the field
> *Physician #4*

Six expressed general support for the gene therapy trial but it's not a priority for them as they have other clinical trials and because of the rarity of the disease and the unknown outcomes, they would rather focus on other work.

> R: No, it's interesting. It's not on the top of my priority because it's a very rare disease, but if any child you can offer good help with and a good outcome. But as I say, if the outcome is getting them to lung transplantation, I'm not sure.
> *Physician # 14*

Intention

***N* = 16**

When asked whether they will participate in this trial to screen and recruit patients. Most (n=11) intended to participate. Those that said they would, cited reasons such as wanting to offer their patients with treatment options when no others exist and wanting to contribute to the evolving science and technology for rare disease.

> R: You know if what we're talking about is just full on SPB deficiency, you know again, we as a group would discuss it before you know moving forward and becoming a site. I don't imagine that being an issue
> *Physician #9*

Three physicians indicated that certain factors might impact their intention to screen including feasibility of recruiting patients, safety data and whether their committee will agree on taking part of the trial.

> R: We can talk about it (research committee), but I think I would need a little bit more experience and data on the trial
> *Physician #12*

In addition, in regard to participate in the trial, two physicians indicated that they would be involved because of their relationship with Dr. Bernard Thébaud, and to support his research.

> R: The only reason I'd be involved is because of Bernard and our relationship. Obviously, we want to help the kids, but I know Bernard very well.
> *Physician #3*

Two physicians said they would not participate in the trial as it is not of interest to them given all the barriers, including lack of resources

> R: I don't think we would be participating in this trial. We would be referring most of these patients to Sick Kids
> *Physicians #11*

Skills

***N* = 15**

Physicians indicated that screening patients for this trial is part of their scope of practice as they would be aware of an infant with SP-B. Only three mentioned that they have the appropriate training regarding clinical trials as their centers are strict with their training. In regard to requesting genetic tests, majority have said they are comfortable with this as again it is part of their scope and additional training is not required for that.

> R: I think if you say that what we need is basically the genetic testing, and this is what we do and what we have access to and we give them out regularly
> *Physician #3*

Social Influence

***N* = 15**

Physician's screening behaviours were primarily influenced by their colleagues (n =10). How and when physicians seek input from their colleagues depends on how a site is structured. Decisions were made first when the research board considers participating in a trial (n = 5). The board evaluates feasibility, and resources required to participate in the trial. Once the decision is made to participate in a trial, participants indicated that all physicians would be motivated to screen and recruit.

> R: Well we work as a team. On our board we have senior nurses and other physicians. We make a presentation showing some of that nice animal data. And after we vote of this is something we want to do.
> *Physician #12*

Once the trial is accepted, physicians noted that they need the opinions from their colleagues before considering enrolling a patient into the study.

> R: I would consult with genetics and respirology. Surgeons potentially, if there will be a transplant. and uh, and the new methodology. To see what the likelihood that the child's going to be eligible. We need to be all connected.
> *Physician #10*

Six physicians (5 pulmonologists and 1 referral site physician) also noted they would need the support from other neonatologists in order to be aware of a possible case and to actively recruit/ consent patients.

> R: A team of neonatologists, they need to inform us of course about those children and make us aware of the case. They see a child in the unit and then we discuss the case together. I would say we would be dependent on the on the neonatology team
> *Physician # 18*

Emotion

***N* = 18**

Majority expressed enthusiasm for this trial. despite the concerns, many (*n*=8) mentioned that this trial will not add additional stress to their workload.

> R: To me no. you know I think it's exciting to think about potential therapy for this.
> *Physician #8*

However, majority (n=10) did mention that it will add additional stress, but it would not impact their ability to participate in this trial. In fact, many mentioned that the stress comes with the job, and it is nothing that they cannot handle.

> R: Of course, it will ass stress, everything does. None of us have time, but it's if it's an important study and it's going to take a baby who would die otherwise. That that's what we do. Why we do what we do right?
> *Physician #3*

Memory, Attention and Decision Making

***N* = 1**

<u>Decision Making</u>

When discussing the factors that might impact their decision to screen, only one physician indicated that they would want to consider how other participants reacted to the experimental treatment. This was an important factor when deciding if they should approach a family with SP-B.

> R: Personally, if I had a patient with surfactant protein B deficiency, whose family was fully on board for transplant, I would feel better knowing that other babies with the same disorder whose parents did not do transplant received the AAV vector first and get a sense of what their responses were
> *Physician #5*

Optimism

***N* = 6**

Of the participants that responded, most (*n* = 6) were optimistic about the trial and expected more good things than bad from the trial results

> R: I hope so. We are at this phase of research because it's based on information already that provides us with hope
> *Physician #5*

Reinforcement

***N* = 16**

Majority of physicians (*n*=14) was involved in the process of prospective patients for clinical trials. Screening for SP-B patients differed from physicians to physicians as only nine physicians indicated that they have seen very few patients with SP-B in their whole career.

> R: Yeah, I think I have two cases of surfactant B deficiency, so in my 40 years I have two cases of surfactant B deficiency.
> *Physician # 6*

Social/Professional Role and Identity

***N* = 12**

Doctors (*n* = 10) stated that screening for trials was part of their role, despite the noted workload associated with screening for trial eligibility. Some noted that their sites do not have a clinical research team (*n*= 2) like others and the physicians take on the role of screening participants. Most physicians believed it was their responsibility to screen patients for eligibility given that clinical trials are commonly used as last resort treatments and many research assistance cannot answer more of the technical questions involved with gene therapy (*n*=10).

> R: It's a phase one study right. Most parents would probably want to speak with the attending physician about it given the complexity of the disease.
> *Physician #11*

Four physicians described in tandem with the clinical research team (research coordinators) whereby the attending physician would be responsible for identifying and pre-screening patients, while the research staff would be responsible for providing detailed study information, obtaining consent from patients and coordinating other aspects of clinical trial participation (e.g., tests, samples, follow-ups), and sometimes engaging in screening procedures.

> R: Screening should be done by both. Because a research assistant associate will not be able to answer questions derived from the testing. So, it should be both
> *Physician #13*

Chapter 5: General Discussion

The impetus for this thesis came from the substantial, unmet needs to improve neonatal regenerative medicine clinical research. The qualitative studies we have conducted aim to identify the barriers and enablers to early phase neonatal regenerative medicine trial participation across a range of stakeholders and mapped them to the Theoretical Domain Framework (TDF) domains, to inform ways of improving trial execution. Neonates are a vulnerable group in the pediatric population. Due to their accelerated development process through their NICU stay, they are usually neglected of treatment options catered to their disease profile, and physicians opt to give treatment well established in the adult/ pediatric populations[1]. Since neonatal research is specific to a disease, only few a participants tend to be available which makes performing clinical research in these little ones more difficult[1]. Thus, in this thesis we aim to identify areas of focus for improving neonatal trial development, recruitment, and trial completion. Given the limited literature on implementation of regenerative medicine therapies in the NICU, it was clear the next actionable step was to integrate perspectives from key stakeholders (neonatal parents, research personnel and physicians) into our upcoming early phase trials; the umbilical cord derived mesenchymal stromal cells (uc-MSC) and adeno-associated virus (AAV) gene therapy trials. I drew on theories of behaviour, as they can provide the framework for synthesizing factors associated with early phase trial execution, hoping to form evidence-based trial interventions, which can be used by other clinicians to establish their trials[2–6].

For all three studies included in this dissertation, we used the TDF to identify barriers and enablers to trial participation, screening, and recruitment for neonatal trials. We initially focused on addressing knowledge gaps parents have discussed when deciding to participate in an early phase stem cell trial[7]. We developed and tested an informational animated educational video to be used as a consenting tool for parents for our future Phase 1 uc-MSC trial. Furthermore, we investigated behaviours related to research staff participation for a planned uc-MSC multi-center trial across Canada. We also showed the participants the animated video to get their thoughts and opinions on the recruitment tool. Lastly, we aimed to identify barriers and enablers to trial participation for a planned AAV trial. Gene therapy is a relatively a new treatment option in the field; it was important to discuss our trial plan with physicians who have experience with surfactant protein-B deficiency in children.

In this chapter, I summarize key findings from each study and aim to compare these findings to highlight overlaps and gaps between the studies. Table 1 showcases the key TDF domains for each study. Furthermore, I hope to provide the foundation exploration of trial participation and execution for early phase regenerative medicine neonatal trials.

Table 1. Key relevant domains for each study

TDF Domains (TDF-V1 & V2)	Chapter 2- Study 1 (parental interviews)	Chapter 3- Study 2 (Research personnel interviews)	Chapter 4- Study 3 (physician interviews)
Knowledge	**X**	**X**	**X**
Skill			
Social/professional role and identity			**X**
Beliefs about capabilities	**X**	**X**	
Optimism			
Beliefs about consequences	**X**	**X**	**X**
Reinforcement	**X**		
Intention	**X**	**X**	**X**
Goals	**X**	**X**	**X**
Memory, attention, and decision making	**X**		
Environment context and resources	**X**	**X**	**X**
Social influences	**X**	**X**	**X**
Emotion			
Behaviour regulation		**X**	
Nature of Behaviour		**X**	

Overall Summary of Findings from Study 1 (Chapter 2)

Chapter 2 reports the findings from a qualitative study involving an important stakeholder group, the NICU parents. Drawing from Guillot *et al*. findings, our team decided to develop an animated video as an implementation tool to aid parents of neonates understand our treatment for bronchopulmonary dysplasia (BPD) in a hypothetical Phase 1 MSC trial. Using the TDF, we conducted one-on-one semi structured interviews with parents of preterm infants (10 in Arm 1- parents with neonates <28 weeks of gestational age (GA) and mechanically ventilated and 4 in Arm 2- parents with neonates <30 weeks GA and not mechanically ventilated) in the NICU. We were able to identify barriers and enablers to potential parental participation for this trial as well as to evaluate the effectiveness of the animated video on influencing parental participation. We showed parents the Phase 1 consent form first, asked them questions developed using the TDF followed by having them watch the video. We then asked similar questions to understand if the video filled in any knowledge gaps. Prior to producing the video, we integrated behaviour change techniques (BCT) to address the TDF domains that were previously identified in a research article written by Guillot and colleagues, focusing on behaviour changes in neonatal parents[7]. To bring some theoretical coherence to the literature, after interviewing the parents, we mapped the identified barriers and enablers to domains from the TDF. We identified 67 belief statements across

12 domains. The barrier and enablers were mostly mapped to *goals, social influence, knowledge, beliefs about consequence, beliefs about capabilities, reinforcement, intention as well as environmental context and resources, memory, attention and decision making*. The key themes to parents decision making to consent were enabling resources, having parents navigate choice in the face of uncertainty, influence from key experts, and ambivalent intention.

This study described barriers and enablers pertaining to parental participation in an early phase trial, focusing on improving trial recruitment. Essentially, we measured a) TDF barriers before parents watched the video, b) we measured the TDF barriers again after watching the video, c) we checked if the video addresses barriers identified by Guillot *et al*., and d) we identified if new/ existing barriers persist that we need to address prior to the Phase 1 MSC trial launch. As reported in cited literature, the animated video brought clarity to the trial procedures, however speaking with a clinical professional might contribute to a higher participation rate[7,8]. Overall, using the TDF allowed us to develop an animated video to be used as a tool in the consenting process and help identify factors that might affect participation to a MSC trial. Strategies commonly described in other literature include build coalition, the use of feedback to improve the informational video, conduct educational meetings and inform local staff of the importance of the research. There remains opportunity to establish best practices when approaching parents for participation in neonatal research and help guide their decision-making process.

Overall Summary of Findings from Study 2 (Chapter 3)

Chapter 3 reports the findings from a qualitative study involving another important stakeholder group, the NICU research staff. Early phase cell therapy trials face many barriers to successful, timely completion. To optimise the execution of a planned clinical trial of uc-MSC therapy for BPD, we sought NICU research personnel across Canada to identify barriers and enablers that may influence their recruitment. This qualitative study involved one-on-one semi-structured interviews with research personnel in level 3 NICUs across Canada. Interview guides and directed content analysis were framed using the TDF, to identify factors that may impede or enable research staff to recruit for a future multi-centre trial. We reached out to thirteen NICU research centres and interviewed 14 research personnel. We identified 67 belief statements across 13 domains. The barriers and enablers were mapped to *beliefs about capabilities, beliefs about consequences, social influence, goals, intention, social and professional role and identity, knowledge, and environmental context and resources, nature of behaviour and behavioural regulations*. The key themes influencing research personnel recruitment were concerns with risks and benefits of the treatment, influence from colleagues, differences in consenting roles, acquisition of resources, the motivation to screen parents, and other competing priorities.

Research personnel play a key role in recruiting to early phase trials in the NICU, however factors affecting their recruitment activities are under-studied. Integrating this stakeholder group into planning and understanding recruitment strategies for a clinical trial of MSCs in neonates can help with optimizing recruitment. Majority of the participants were excited to hear about the trial and keen to use the animated video as a resource to recruit parents. Similar to literature, the participants were concerned by their colleagues' opinion on the study and mentioned the importance of staff education[4,9]. Suggested strategies to facilitate the planning and delivery of the uc-MSC trial include conducting educational sessions for the staff, promote adaptability, providing

protocol training/ mentorship, and providing and implementing resources to help with trial recruitment. Nevertheless, this study helped bridge knowledge gaps with clinical research staff for our team to prepare them for the upcoming multi-center trials.

Overall Summary of Findings from Study 3 (Chapter 4)

Chapter 4 reports on a qualitative semi-structured interview study with the physicians (neonatologists and pulmonologists) stakeholder group from Canada, America, United Kingdom and Europe. Prior to conducting the first adeno-associated viral (AAV) vector trial to treat surfactant protein-B deficient babies in the world, we used the TDF to map out the identified physician-related barriers and enablers to screening and recruiting patients for an early phase gene therapy trial. We interviewed 18 physicians (13 neonatologists and 5 pulmonologists). We identified 50 belief statements across 13 domains. The barriers and enablers were mapped to *goals, beliefs about capabilities, social influence, knowledge, beliefs about consequence, social and professional role and identity, environmental context and resources, and intention*. The main themes identified to influence trial participation were the capability to screen for patients with clearly defined study procedures and outcomes, acquisition of resources and differentiating recruitment roles, and having cautious hope. This novel study shows the most in-depth comprehensive analysis to trial participation from physicians having experience with children diagnosed with SP-B.

The application of the TDF helped identify key potential barriers and enablers prior to executing one of the first AAV trials in babies. Most of the physicians expressed excitement for this study and looked forward to the trial. However, there were key points that needed to be considered prior to study launch, such as involving and recruiting from key SP-B referral sites and increasing awareness in the medical community for this ultra-rare disease. Many expressed the need for staff buy-in when approaching parents, and highlighted variability in screening roles that should be addressed to prevent missing tentative, eligible participants. The results will help to refine the study design and execution of the trial. Suggested strategies to address the barriers and enablers identified were to provide educational sessions including recruiter training, educational tools, and distributing diagnostic tools. This approach can optimize trial procedures and help other clinicians with their early phase gene therapy trials.

Comparison Between Findings from each Study

Identified Themes from the TDF

The Theoretical Domain Framework (TDF) can be a useful framework to facilitate behaviour change in research participants[2,5,13,14]. The TDF proved to be a useful framework in this thesis, as it helped to investigate barriers and enablers at the individual level across groups and providing consistency in trial planning[14].

Upon mapping the theoretical themes to the TDF, the following domains were identified throughout the three-studies: *beliefs about consequences, intentions, social influence, knowledge, and environmental context and resources, and goals*. All three studies had minimal representation for *emotion, optimism, and skills*.

While examining the coverage of TDF domains, similar themes were identified between all three studies. For example, for themes mapped to *beliefs about consequences*, the belief surrounding the 'expected outcomes' from the therapeutic treatment options as well as 'safety and efficacy' of the treatments were voiced by all three stakeholders. This domain measured the participants' support for the clinical trials through any 'perceived disadvantages', 'treatment benefits' and 'long-term benefits'. However, Chapter 3 involving research personnel, contributed additional themes mapped to the *beliefs about consequences* including 'overwhelming parents with multiple research studies'. Chapter 4 (involving physicians) identified perceived disadvantages mapped to *beliefs about consequences* including difficulty with 'ethics submission process' and 'lack of SP-B patients' for recruitment. Both studies added an in-depth analysis with themes, describing importance of 'educating clinical staff', to the success of the trial and staff members 'workload', while recruiting for various studies. Concerns about the study design, such as 'lack of patients' and 'different site practices', were voiced by the physician stakeholder group as barriers. A common concern for physicians was the scarcity of standard of care for SP-B, which was not a concern for the BPD stakeholder groups due to other treatment options. Nevertheless, the key themes focused on, to prevent any obstruction of trial completion, include treatment benefits and implications.

For themes mapped out in *goals,* the beliefs surrounding 'motivators-improving the child's health' and 'advancing science' were seen in all three groups. There were additional themes reported by the research personnel group, one being competing priorities to their involvement in the hypothetical uc-MSC trial. Another theme identified from this stakeholder group includes 'achieving recruitment goals' as an enabler. Chapter 4, which focused on the physicians' priorities to be involved in the AAV gene therapy trial, also mentioned 'concerns for their patients' as an enabler subtheme. Since Chapter 4 focuses on a rare disease with no treatment option available, a key motivator is giving parents an experimental treatment option that may prolong their child's life. All three studies added a closer look into themes describing priorities that reflect the participant's desire to be part of the trial.

The *social influence* domain was captured by all participants in the three studies. The findings point to the 'importance of influence other clinical staff' on trial participation. For example, the educating other clinical staff, bringing awareness to bedside nurses and other clinical physicians (other neonatologists, charge nurse and colleagues) on trial conduct. Both the research personnel and physician's stakeholder groups mentioned 'support from colleagues' as an enabler to screening/ recruiting trial participants. Interestingly, in Chapter 2, parents asked to hear the study from the physicians rather than the recruiters. This was also seen in Chapter 3 and 4, the research staff and physicians noted that physicians should be involved in the recruitment process as a support, to answer knowledge heavy questions from the parents. Parents did mention opinions of medical professionals was an enabler to trial participation. 'Perception of the video' was another theme mapped under *social influence* in Chapter 2 and the inclusion of the regulatory bodies in addition to having the lead Principal Investigator narrate the video added accountability of the study design. Demonstrating solid leadership from the study leader is seen as a successful implementation effort[15]. Nevertheless, the key themes focused on *social influence* and its effects on trial participation/ recruitment are important to focus on when executing our trials.

For themes mapped to the *knowledge* domain, the belief surrounding 'existing knowledge of the disease of interest' were captured by all three study participant groups. Chapter 3 (research personnel) and Chapter 4 (physicians) contributed similar themes mapped to the *knowledge* domain with 'existing procedural knowledge' and 'existing therapeutic treatment knowledge', indicating that these two stakeholder groups are familiar with the recruitment procedures and the clinical treatment involved for both BPD and SP-B. This is a common theme for both groups, as clinical research is part of their scope of practice and associated with their professional roles. Few parents in Chapter 2 did mention understanding the scope of clinical research, which may be due to past encounters. Not surprisingly, all groups, after hearing about the hypothetical clinical trials, wanted to know more information such as preclinical evidence and the outcomes about the treatment of interest.

Key themes observed by all three groups under the *intention* domain, related to their 'intent to participate'. This domain measured their intention to participate in the hypothetical trial that was described to them. The only difference was with the parental stakeholder group, as their intention to trial participation was evaluated twice, once after reading the informed consent form and again after watching the animated video. The focus of Chapter 2 was on improving their understanding of the trial with the use of the animated video compared to solely the consent form. Majority of the participants in each stakeholder group intended to participate in the trial regardless of any perceived barriers.

The themes mapped to *environmental context and resources*, was 'additional resources required to aid in their decision making' and observed by all stakeholders. This domain measured tools for support and environmental factors that may act a barriers and enablers to the participants target behaviour. The research personnel and the physicians expressed similar beliefs mapped to this domain. Due to their professional roles at their respective sites, they mentioned themes that are related to screening and consenting parents for the uc-MSC trial and AAV gene therapy trial. The belief statements involving 'logistical factors playing a key role', 'the need for support and tools' and 'access to funding' were seen by both. The physicians expressed some barriers related to 'physician workload and time' and the 'rarity of the disease' that may impact their decision to participate in the trial. The research personnel also voiced requiring access to tangible information, including the video as a consenting tool. Parents also appreciated having the animated video tool available to better understand the trial.

When examining all three studies coverage of TDF domains within themes, it was clear many relevant beliefs identified between studies were not relevant, as the target behaviours for each study were different. For example, for themes mapped to *beliefs about capabilities* domain, where the groups involving research personnel and the physicians, captured beliefs surrounding the 'act of screening and enrolling patients', whereas for parents, beliefs were surrounding 'their confidence to participate in the trial'.

Main themes identified, such as 'perception of recruiting/ screening roles' and 'variability of screening roles' was mapped to *social/ professional role & identity* domain in Chapter 3 & 4, with focus on research personnel and physicians. Similar themes pertaining to screening/ recruiting roles highlighted one's professional role within the research community. Although in

Chapter 3 this domain provided limited information factors driving broad beliefs and attitudes towards trial participation/ recruitment/screening.

There were some barriers and enablers identified in the parent regarding the *reinforcement* domain, that was not captured in research personnel. 'Experience with previous clinical trials' was mapped to *reinforcement,* as this domain focuses on increasing a response to stimuli. This theme is seen with research personnel, but is mapped under *behavioural regulation,* as this pertains to their daily role(s). Although this provides more insight to one's decision-making process towards trial participation/ recruitment, it is subjective to one's experience with clinical trials and is not considered a key theme. Similar to the domain *optimism,* stakeholders' opinions during this trial are subjective to one's experience and provides limited information about the factors driving broad beliefs and attitudes towards trial participation/ recruitment/screening. Future research should investigate this domain.

A general measure of identifying themes for one's intent for trial participation, screening and recruitment include safety/ efficacy of the treatment, motivators, opinions from key figures, and the need for additional resources. The qualitative in-depth analysis provides awareness and the knowledge to optimize trial recruitment and completion. There is still the need for additional investigation required of how relevant certain barriers and enablers are to trial participation/ recruitment/ screening to active studies, as all three studies have given the participants hypothetical scenarios. It will be useful to investigate the influence of these barriers/ enablers discussed throughout the thesis on the intent to participate in an early phase clinical trial.

Additional Domains and Themes Identified

There was minimal representation in*; memory, attention and decision-making processes; emotion; nature of behaviour, behavioural regulation and skills*. Chapter 2, involving the parent stakeholder group, highlighted various key enablers mapped to memory attention and decision-making. Factors that mapped to this domain, 'cognitive recall' and 'factors including decision-making', were important to the parents in their consideration of trial participation. Parents preferred the animated video, as it helped to educate them on the study procedures, ultimately aiding in their decision-making. Themes related to *emotion* were minimally represented in all three studies. There were few themes related to 'positive perception' of the animated video for the parental group and 'stress' of workload for the physician group but neither were identified as an enabler and or a barrier. Moreover, the research personnel group was only represented by *nature of behaviour* and *behavioural regulation*; domain(s) *nature of behaviour* encompasses the theme of experience with clinical trial recruitment, whereas *behavioural regulation* identified the theme of planned approach to potential participants. These two domains are the cornerstone to research personnel target behaviour, involvement in trial recruitment, thus not seen in parents and physicians' responses. For the research personnel group, factors involving 'previous research experience' mapped to *nature of behaviour* and was a key factor in their ability to recruit participants for the uc-MSC trial. Many had experience with early phase trials, thus recruiting for this Phase 1 trial did not seem out of their scope. This was also noted in the *skills* domain, seen in both Chapter 3 and 4 however, pertains to any formal recruitment training and recruitment skills related to the work of physicians and research personnel. However, the themes 'approaching skills for consent' and 'formal training' provides limited information about the factors driving broad

beliefs and attitudes towards trial participation/ recruitment/screening. Nevertheless, the lack of representation of these domains by other stakeholder groups should be addressed in future studies.

Implication for future research

Researchers currently lack guidance on how to optimize the delivery of clinical trials in neonates, and lessons can be learned and further applied from this dissertation. The unique barriers and enablers have been neglected by researchers in qualitative literature, as the focus has been understanding the factors related to trial participation, rather than understanding the specific barriers and enablers from the key stakeholders. The key recommendation derived from this thesis focuses on the facilitation and delivery of early phase clinical trials are mentioned below. The recommendations come from summarizing the main themes derived from the TDF domains, identified as barriers and enablers to trial participation and execution. The barriers and enablers, underlying beliefs and suggested actions identified could be used to inform how to tailor interventions for clinical staff prior to trial launch.

Collecting data from key stakeholders early in trial development

The main correlation between all three studies is the of involvement of multiple stakeholders (NICU parents, research personnel, and physicians) to ensure feasibility of conducting early phase regenerative medicine clinical trials in neonates. When developing a clinical trial, it can be helpful to factor patients' and other stakeholders' views, as they have valuable expertise and experience that can inform optimising recruitment strategies when carrying out the trial. Speaking with the stakeholders about their thoughts and opinions of the trial design from the start is essential to developing and conducting a trial, and important to overcome barriers prior to trial execution[4,6–10]. In the case of trial participation, we believe that it is important to consider the perspectives of all those who have a stake in the intervention, from designers (trial clinicians and trial research staff) to consumers (potential trial participants and deliverers such as research assistants). Having a "user-centered" approach, which optimizes the "users" hypothetical involvement experience, helps develop guidance while creating a robust clinical trial[11]. The collaboration of all three groups allowed us to incorporate their views into the trial design, aligning with groups' preferences and representation[11,12]. The analysis of the identified themes from the groups responses to these interviews provides feedback to other clinicians in their trial development, evidence for improving the execution of early phase clinical trials and opens avenues to patient-centered tools.

Our research discovered themes related to trial planning and development. The intended sites for the inclusion of early phase clinical trials should be contacted early to determine and increase engagement from site personnel (including lead investigators, research assistants, coordinators, and representatives from the patient group). Incorporating these important groups early into trial development is important as the stakeholders experience can provide valuable feedback to improve trial design and ultimately, they will positively advocate for the research to their team[8–10]. The findings in this thesis shows that participant barriers should not be assumed but rather should be addressed. Results from this thesis indicate that by being proactive, identifying and addressing unknown barriers and enablers before trial launch will be beneficial to the trialists.

For example, we created an animated video in response to parents expressing the need for having a different communication strategy to discuss the Phase 1 uc-MSC trial[7]. By doing so, the parents may be more receptive to hearing about the trial from the clinical research staff and be keen on participating. Having a multi-media tool not only helps parents understand the trial in-depth but can help clinical staff to understand the importance of the trial[19–22]. Co-development of educational tools ensures that concerns are addressed in a comprehensive manner, and other trialists can incorporate this tool into their study design.

Promote networking to enable support for the trial

Many participants from all three studies noted the influence that clinical staff have on trial participation, not limited to parents but also to bedside nurses. With increased communication and education for the clinical staff about the study, discussing the importance of the research will help them advocate to potential trial participants and fellow colleagues[4,8]. As mentioned before, the lead investigator should provide informational sessions to the nurses and other physicians to help advocate for the trial[17]. Majority of the participants wished to know more the therapeutic treatment including preclinical evidence of the effectiveness of the treatment. Our findings could serve to bridge specific knowledge gaps that should be targeted in educational components within the interventions. Specifying the difference between standard of care and the treatment, as well as stating the importance of stakeholder involvement, can help improve the recruitment rate for early phase clinical trials[3,15,23]. This was demonstrated in Chapter 3 (research personnel stakeholder group), where one of the participants mentioned that by bringing the uc-MSC trial to the unit's research board, which included members from the head of neonatology, nursing, and respiratory therapist team(s), would help to encourage and implement the trial at the hospital.

Ensure there are adequate resources (including support and finances) for sites to participate in the trial

A key barrier that was identified for sites to participate was the limit of available resources, including finances, study personnel and diagnostic tools. Specifically for early phase regenerative medicine trials, there is a need to provide adequate training and materials to the study staff to perform the trial procedures[7]. It is important to note that adequate funding is available to support active sites for their needs and wants. Sites should be chosen based on the number of researchers available and the resources their institution can provide, thus not hindering the lead investigators budget. Furthermore, providing support to the clinical team is essential and addressing their needs and wants will ensure their site is equipped with all the resources to perform the trial smoothly.

Contribution of Thesis to Future Intervention Development

For years, neonates have been "therapeutic orphans" and denied the benefits of clinical research because most therapeutic options are usually tested in the adult population[24]. The need for effective interventions to increase trial participation and execution is required to help accelerate neonatal research. Many neonatal trials are neglected of therapies that are suited to the disease profiles that this patient population faces[18]. There are very few articles reporting on trial optimisation for early regenerative medicine in the adult population and almost none in the neonatal population; there is a lack of literature on the execution of early phase clinical trials in the neonatal population[19,20] The primary objective of the studies included in this thesis were to

investigate barriers and enablers to trial participation and trial recruitment for an uc-MSC trial and patient screening for an AAV gene therapy trial. Researchers currently lack guidance on how to optimize trial recruitment and early phase trial completion and lessons can be learned from this thesis. Our research contributes to intervention development by using the TDF to identify and tackle barriers and enablers to trial participation. The recommendation derived from this dissertation serves to inform trialists to design a robust clinical trial and facilitate the use of a multi-media tool to provide all the informational needs to trial participants. While strategies were identified for the defined barriers and enablers for each study, the studies were not designed to formally test the different strategies. The main themes, barriers and enablers identified throughout the dissertation help inform how to operationalize each theme. This thesis also emphasizes the importance of facilitating behaviour theory in developing interventions. Researchers can use behaviour theory to develop novel interventions catered to their own research trials.

Strength and Limitations

The strength of this study lies in the use of the TDF to identify factors that may impact physicians and research personnel screening and recruiting behavior as well as NICU parents decision-making behaviour. The TDF gave a comprehensive assessment of the potential barriers and enablers to screening, recruiting and decision-making to an early phase AAV gene therapy trial and uc-MSC clinical trial. By using the TDF, which encompasses a wide range of theories into one framework, the focus was placed on the target behaviour which was being studied. By linking the research findings to the therapy, it allowed us to generate evidence-based strategies that other trialists can use as well. It first allowed us to identify a vast array of theory-based factors associated with trial participation and assisted in trial development. It also brought theoretical coherence to literature and allowed us to identify key research gaps and opportunities to test new strategies to address the barriers and enablers.

Despite conducting qualitative semi-structured interviews to understand barriers and enablers, one limitation is conflict of interest that may arise when stakeholders of highly invested participants see the benefits of the research rather than those who declined to participate. From this, the stakeholders communicated and expressed their views, which reflect the perspective(s) of potential trial participants. The findings from the participants interviewed also reflected specific perceptions driven by a lack of treatment options associated with the given disease. Another limitation is gender bias, as most participants were women in the research personnel group compared to physician group which were mostly men. The underrepresentation of both genders in each stakeholder group can affect the overall themes identified throughout the interviews. Future research should have equal representation to obtain better all-around results.

The interviews were semi-structured, and participants in the interviews were invited to express any other concerns or thoughts. They were allowed the freedom in their replies to discuss other aspects of the trial execution. The participants were given a hypothetical scenario of participating in the trial, and we captured hypothetical barriers and enablers. There is the potential of missing determinants and therefore trialists must be cautioned that the qualitative studies were specific to neonates and the disease of interest. Hence, the findings may not be comparable to other clinical studies. However, since neonatal regenerative medicine is a novel topic, a comprehensive interview study elicits more open discussion and understanding for interested parties.

Application of the TDF was valuable in identifying potential barriers and enablers of trial participation from the perspective of three stakeholders: parents, research personnel and physicians. By directly approaching these groups, we were able to identify their preferences on resource needs, trial outcomes and support. Furthermore, the qualitative approach is valuable in confirming interest for the trials.

Conclusion

This dissertation demonstrates the value of using a comprehensive approach to identifying potential trial-specific barriers and enablers prior to conducting an early phase regenerative medicine therapy clinical trial in efforts to optimize trial activities. The methods described (qualitative interviews based on the TDF) and tools (interview guide, animated video) incorporated could serve as an adaptable example that can be used to help future trialists. Identifying and prioritizing barriers most relevant for specific upcoming trials can guide the allocation of training resources used at trial launch and throughout the lifespan of the trial, to support research clinicians. Our findings highlighted the importance of incorporating important stakeholders early on into the trial development process. As promising gene and MSC therapies exist to improve care on incurable lung diseases, it is apparent there is a knowledge gap on the feasibility of conducting early phase regenerative medicine clinical trials in this population. As a foundation for promoting a behaviour theory-based understanding of trial development, this thesis highlights priorities for future research and will contribute to developing novel clinical interventions to increase bench to bedside translation. More importantly, the dissertation aims to advance scientific knowledge and set a foundation of anticipated barriers and enablers to early phase clinical trials in the NICU.

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