Dear Editors,

Enclosed please find the protocol for our study which we have submitted for your consideration for review and possible publication.

This supplement contains the following items:

1. Original protocol, final protocol, summary of changes.
2. Original statistical analysis plan, final statistical analysis plan, summary of changes

There has been no change in the statistical analysis. With respect to the protocol changes, the lower age limit of the included patients was lowered from 6 weeks to 4 weeks since suboptimal saturations/desaturations may play the biggest role in the youngest infants with respect to disposition. The lower limit of the true oxygen saturation for the inclusion criteria was lowered from 90% to 88% to expand the potential impact of the intervention in well looking infants with mild hypoxia. For safety reasons, the alarm was programmed to go off at a displayed saturation of 92%, since many physicians tend to intervene in children with saturations at this level. Since chronic lung disease of prematurity constituted an exclusion criterion, prematurity as such should not play a major role in otherwise healthy infants with bronchiolitis and this criterion was therefore eliminated.

Yours Sincerely

Dr Suzanne Schuh
### Project Application—Thrasher Research Fund

**Title**
Impact of Oximetry on Disposition in Acute Bronchiolitis

#### Principal Investigator
Suzanne Schuh  
c/o The Hospital for Sick Children  
Department of Emergency Medicine  
555 University Ave.  
Toronto, ON  M5G 1X8  
Canada

**Co-principal Investigator(s)**
- Stephen Freedman – The Hospital for Sick Children
- Allan Coates - The Hospital for Sick Children
- Patricia Parkin - The Hospital for Sick Children
- Upton Allen - The Hospital for Sick Children
- Andrew Willan - Research Institute, The Hospital for Sick Children
- Wendy Ungar – Research Institute, The Hospital for Sick Children
- Zelia Da Silva - The Hospital for Sick Children

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416-813-6239  
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416-813-5043

**E-mail**
Suzanne.Schuh@sickkids.ca

#### Human Subjects?
- **Form Status**: Included
- X Yes  
-  
- No

#### Animals Used?
- **Form Status**: Pending
- Yes  
-  
- No

#### Project Period
- The entire project may not exceed 3 years. The project start date will be determined in consultation with Thrasher Research Fund staff.

**Approximate start date (month and year)**
December 1, 2007

**Approximate end date (month and year)**
April 30, 2010

**Total Budget Request**
$285,136

#### Performance Site(s)
Indicate where the work described in the “Experimental Design and Methodology” section will be performed. Please provide specific organization names and their complete addresses, including zip/postal code, telephone number, fax number, and email.

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| The Hospital for Sick Children  
Pediatric Emergency Department  
555 University Ave.  
Toronto, ON  M5G 1X8  
Canada  
Tel: 416-813-5807  
Fax: 416-813-5043 | The Hospital for Sick Children  
Pediatric Emergency Department  
555 University Ave.  
Toronto, ON  M5G 1X8  
Canada  
Tel: 416-813-5807  
Fax: 416-813-5043 |

#### Supervising Institution
Name the one organization that will be legally and financially responsible and accountable for the use and disposition of any funds awarded on the basis of this application.

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<th>Supervising institution name and address</th>
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| The Hospital for Sick Children  
555 University Ave.  
Toronto, ON  M5G 1X8  
Canada | (416) 813-5723 |

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<td><a href="mailto:AnneMarie.Christian@sickkids.ca">AnneMarie.Christian@sickkids.ca</a></td>
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#### Official Signatures for Supervising Institution
We, the undersigned, certify that the statements herein are true and complete to the best of our knowledge and that facilities are available for the proposed research. We will comply with the Thrasher Research Fund’s Conditions of Grant and requirements for reporting that are in effect at the time of the award.

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<th>Name and title of principal investigator</th>
<th>Signature</th>
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| Suzanne Schuh  
Staff Emergency Physician and Research Director  
Division of Pediatric Emergency Medicine  
Senior Associate Scientist, Research Institute  
Professor of Pediatrics, University of Toronto | | |

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<td>Chairman, Department of Pediatrics</td>
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<td>Ms. Anne Marie Christian</td>
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<td>Vice President, Research Operations</td>
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<td>Associate Chief, Research Institute</td>
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Protection of Human Subjects Assurance/Certification/Declaration
Thrasher Research Fund

**Policy** A research project involving human subjects sponsored by a U.S.-based institution that is not exempt from HHS regulations may not be funded unless an institutional review board (IRB) has reviewed and approved the activity in accordance with Section 474 of the Public Health Service Act as implemented by Title 45, Part 46, of the Code of Federal Regulations (45 CFR 46-as revised). The applicant institution must submit certification of IRB approval to the Thrasher Research Fund unless the applicant institution has designated a specific exemption under Section 46.101(b) that applies to the proposed research project. Institutions with an assurance of compliance on file with HHS that covers the proposed project should submit certification of IRB review and approval with each application. In the case of institutions that do not have an assurance of compliance on file with HHS covering the proposed project, certification of IRB review and approval must be submitted within 30 days of the receipt of a written request from HHS for certification. Documentation of IRB approval from all project-related participating institutions must be included.

**Title of application** Impact of Oximetry on Disposition in Acute Bronchiolitis

**Principal investigator** Suzanne Schuh

**Investigational New Drug Exemption** If more than one is involved, list others under notes below.

**Food and Drug Administration required information** In accordance with 45 CFR 46.121, if an application is made to HHS requiring certification and involving use of an investigational new drug or device, additional information is required. Thirty (30) days must elapse between date of receipt by FDA of Form FD-1571 and use of the drug, unless the 30-day delay period is waived by FDA (21 CFR 312.1).

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**HHS Assurance Status**

- [ ] This institution has an approved assurance of compliance on file with HHS which covers this activity.
- [ ] No assurance of compliance which applies to this activity has been established with HHS, but upon request the applicant institution will provide written assurance of compliance and certification of IRB review and approval in accordance with 45 CFR 46.

**Certification of IRB Review or Declaration of Exemption**

- [ ] Certificate has been reviewed and approved by an IRB in accordance with the requirements of 45 CFR 46, including its relevant subparts. This certification fulfills, when applicable, requirements for certifying FDA status for new investigational drug or device.

**Date of IRB approval** (If approval is pending, write "pending.")

- [ ] Full Board Review
- [ ] Expedited Review

**Notes**
American Academy of Pediatrics (AAP) bronchiolitis guidelines suggest that infants with oxygen saturation of 90% and above should be admitted, and several authors question the benefits of relying mainly on oxygen saturation for hospitalization. Recent preliminary evidence suggests that this change in practice may be at least in part responsible for this dramatic increase in hospitalization, often irrespective of the amount of breathing distress the child is in. Numerous infants with only mild discomfort and a mild decrease in saturation who previously would have been discharged home are now being admitted.

Preliminary evidence suggests that this change in practice may be at least in part responsible for this dramatic increase in admissions, and several authors question the benefits of relying mainly on oxygen saturation for hospitalization. Recent American Academy of Pediatrics (AAP) bronchiolitis guidelines suggest that infants with oxygen saturation of 90% and above are unlikely to benefit from supplemental oxygen and call for studies on the most efficient use of oxygen and of oximetry monitoring. However, this recommendation is based on physiologic principles and has not been tested in practice. This is the first study seeking to examine if the hospitalization decision in bronchiolitis should be determined primarily by clinical assessment and if infants who are otherwise well enough to go home whose saturation is above or in the vicinity of that recommended by the AAP for supplemental oxygen therapy can be safely discharged.

The primary objective in previously healthy infants diagnosed with acute bronchiolitis in a pediatric emergency department (ED) to compare the rate of hospitalization within 72 hours in those whose oxygen saturation measurements are set consistently 3% above the true values versus those in whom saturation measurements represent true values.

To date, only two studies of oxygen saturation in bronchiolitis have been done; one consisted of a survey using imaginary clinical scenarios and the other was a retrospective inpatient study. The former study showed that a physiologically unimportant difference in saturation of 2% would potentially result in a two-fold difference in hospitalization. Our study should answer whether this indeed happens in real life and whether the discharge decision should be decided primarily clinically. The latter paper demonstrated that hospitalized infants with bronchiolitis who meet clinical discharge criteria stay in hospital on average an extra 1.6 days due to persistent mild decrease in oxygen saturation.

Design. Previously healthy infants 6 weeks to 12 months of age with bronchiolitis and with saturation ≥90% will be eligible. Children with severe bronchiolitis, other significant illnesses or prematurity will be excluded. They will be randomized to undergo management with intermittent oximetry using either true oxygen saturation measurements or saturation measurements set three percentage points above true values. Neither physicians, parents or study nurses will be aware of the group assignment, i.e., they will not know if the saturation measurement displayed corresponds to the true value. Primary outcome will be the rate of hospitalization within 72 hours in the two groups. Secondary outcomes will include the rate of supplemental oxygen therapy, unscheduled visits for bronchiolitis within 72 hours, length of ED stay and economic analysis.

Potential Impact. This study will have immediate impact on management. Based on the results we should find out if clinical assessment should play a primary role in the decision regarding disposition and if children who are otherwise well enough to go home and have saturations above or close to the threshold recommended by the AAP can be successfully discharged. It will also hopefully shed some light on the probability of therapeutic failure (i.e., admission within 72 hours) in children whose oxygenation is within a relatively narrow range of the safety limits recommended by the AAP, thereby eliminating the bias to admit created by the presence of mild and clinically insignificant decrease in oxygenation. If the current practice of oximetry with the highly variable and higher thresholds for oxygen therapy indeed significantly contributes to the alarming rise in hospitalizations in bronchiolitis, proper use and interpretation of this technology may lead to fewer hospitalizations and thereby reduce the burden on the children and their caretakers.
Objectives/ Specific Aims – Bronchiolitis is the most common lower respiratory tract infection in infants, responsible for 90,000 hospitalizations annually, at a cost of $700 million US. Since 1980, the proportion of children hospitalized for bronchiolitis has risen by 25% while mortality has remained unchanged. Since 20 years ago infants with bronchiolitis have been routinely undergoing oxygen saturation monitoring, the results of which are then used to decide on supplemental oxygen therapy. The threshold for giving supplemental oxygen varies widely from 90 to 94% and depends on local practices due to lack of evidence-based guidelines. Over the years saturation has even become one of the main criteria for hospitalization, often irrespective of the degree of respiratory distress. Numerous infants with minimal distress and mild hypoxia who previously would have been discharged are now being admitted. Preliminary evidence suggests that this change in practice may be at least in part responsible for this dramatic increase in admissions, with physicians assigning greater significance to oximetry than to the physical examination. However, it is limited by retrospective design and by the use of hypothetical vignettes. Specifically, postulated saturation of 92% resulted in 83% planned admission rate, which was double the hospitalization rate for saturation of 94%, irrespective of the degree of respiratory distress. Experts question the merits of the frequent use of oximetry and of relying primarily on saturation as a criterion for disposition. Recent American Academy of Pediatrics (AAP) bronchiolitis guidelines suggest that previously healthy infants with oxygen saturation of 90% and above are unlikely to benefit from supplemental oxygen and call for studies on the most efficient use of oxygen and of oximetry monitoring. We hypothesize that the hospitalization rate of children who according to the ED physicians meet clinical criteria for discharge and whose saturation display has been falsely increased by three percentage points above the true values will be significantly lower than that of their counterparts whose physicians are presented with the true measurements. We plan the following specific aims:

1. To determine if there is a significant association between the difference in the primary outcome between the groups and the study procedure. Screening for eligibility and consent will take place in the ED triage. True oxygen saturation of eligible infants will be taken by the study coordinator and will only be entered in the patient chart in the event of non-participation or after conclusion of the intervention. After enrolment, the patients will be randomized by an internet randomization service to those undergoing hourly saturation monitoring using either true oxygen saturation measurements or measurements which have been set 3% above the true values, the research nurse, ED staff and parents will thus be blinded to true saturations. Enrolled children will be observed for at least approximately 3 hours. The ED physicians will be encouraged to use supplemental oxygen based on their clinical assessment (irrespective of the saturation) and their interpretation of the displayed saturation measurement. All children will receive one standardized dose of nebulized albuterol 2.5mg/dose. Primary outcome will be hospitalization within 72 hours, defined as admission to our inpatient ward, transfer to another inpatient facility or the need for bronchiolitis therapy at the index visit lasting more than six hours. Secondary outcomes will be supplemental oxygen therapy, length of stay in the ED and unscheduled return for care within 72 hours; an economic assessment will also be done. The research coordinator will assess the oxygen saturation, respiratory rate, RDAI score and the disposition plan at baseline and hourly thereafter up to 360 minutes or disposition, whichever comes first. He/she will also measure the secondary outcomes and collect the data needed to estimate costs/savings in the two groups. Unscheduled return for care and delayed hospitalizations following initial discharge will be determined during telephone follow-ups at 72 hours.

2. To determine if there is a significant association between the difference in the primary outcome between the groups and the patients’ age and disease severity.

3. To determine if there is a significant association between the difference in the primary outcome between the groups and the patients’ age and disease severity.

4. To determine the incremental costs/savings gained from the societal perspective in the two study groups.

Methodology

Study design: Randomized double blind single center trial.

Study population: Previously healthy children aged 4-12 weeks to 12 months of age with the first episode of acute bronchiolitis, with baseline Respiratory Disease Assessment Instrument (RDAI) ≥3 and true oxygen saturation ≥90%.

Exclusion criteria: Pre-existing pulmonary or cardiac disease, neuromuscular disease or chronic hypoxia, severe respiratory distress (retraction component of RDAI ≥6 out of 9 points), room air oxygen saturation <88%, history of prematurity or unavailability of telephone.

Study procedure: Screening for eligibility and consent will take place in the ED triage. True oxygen saturation of eligible infants will be taken by the study coordinator and will only be entered in the patient chart in the event of non-participation or after conclusion of the intervention. After enrolment, the patients will be randomized by an internet randomization service to those undergoing hourly saturation monitoring using either true oxygen saturation measurements or measurements which have been set 3% above the true values, the research nurse, ED staff and parents will thus be blinded to true saturations. Enrolled children will be observed for at least approximately 3 hours. The ED physicians will be encouraged to use supplemental oxygen based on their clinical assessment (irrespective of the saturation) and their interpretation of the displayed saturation measurement. All children will receive one standardized dose of nebulized albuterol 2.5mg/dose. Primary outcome will be hospitalization within 72 hours, defined as admission to our inpatient ward, transfer to another inpatient facility or the need for bronchiolitis therapy at the index visit lasting more than six hours. Secondary outcomes will be supplemental oxygen therapy, length of stay in the ED and unscheduled return for care within 72 hours; an economic assessment will also be done. The research coordinator will assess the oxygen saturation, respiratory rate, RDAI score and the disposition plan at baseline and hourly thereafter up to 360 minutes or disposition, whichever comes first. He/she will also measure the secondary outcomes and collect the data needed to estimate costs/savings in the two groups. Unscheduled return for care and delayed hospitalizations following initial discharge will be determined during telephone follow-ups at 72 hours.
**Hypothesis(es) and Aims**

State concisely the hypothesis(es) to be tested and the specific aim(s) of the project. Do not exceed one page.

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**A. Hypothesis(es) to be Tested**

Preliminary evidence and expert opinion suggest over-reliance on oximetry in the disposition decision in bronchiolitis and the likely contribution of this practice to the recent dramatic rise in hospitalizations in this disease. If this is so, blinding the ED physicians to oxygen saturations and by falsely raising the displayed values by an amount which is physiologically insignificant but widely perceived to be clinically relevant should result in hospitalization rates which are significantly lower than in those whose physicians are presented with true saturations. In this randomized double blind trial we hypothesize that previously healthy infants with bronchiolitis whose emergency department physicians are blinded to true oximetry measurements and in whom the oximetry measurements are elevated three percentage points above true values will have hospitalization rates within 72 hours of presentation at the index visit at least 15% lower compared to those whose physicians see true saturations. The impact of this intervention will also be assessed by comparing the proportions of infants receiving supplemental oxygen, unscheduled medical visits within 72 hours of presentation, length of stay and the incremental costs/savings in the two groups.

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**B. Specific Aim(s) of the Project**

1. In previously healthy children with bronchiolitis undergoing hourly oximetry measurements, to compare the rate of hospitalization within 72 hours of presentation in those whose emergency physicians are presented with true oxygen saturation measurements versus those whose oxygen saturation measurement display is raised 3% above respective true values. Hospital admission constitutes an important outcome since it carries a major impact on the family and the health care system. However, for clinicians to accept that children with bronchiolitis who have saturation in the vicinity of 90% or higher and who otherwise meet discharge criteria can be sent home, not only must it be shown to be effective but it must also be safe. Although previous studies have found that a mild reduction in oxygenation is linked to progression of disease severity, they have not employed specific protocols focusing on this critical issue. We shall assess this by comparing the proportions of hospitalizations either at the index ED visit or within the next 72 hours since this later group clearly will not have been successfully discharged. Hospital admission within 72 hours thus incorporates the outcome of both the immediate disposition and safety. This will be the first randomized double-blind controlled trial examining clinical impact of blinding the emergency physicians to true oxygen saturations by presenting them with either true or falsely elevated measurement values. Since the infants in the altered saturation group will have real saturations comparable to those in the true saturation group, finding a significant difference will likely be due to the differential interpretation of displayed measurements in mildly hypoxic children. The study will help us determine if children with bronchiolitis who have saturations around 90% or higher can be successfully discharged. It will also shed light on the frequently asked question if well looking infants with saturations in the very high 80s/low 90s are at a high risk of subsequent admission to hospital.

2. To compare the rate of supplemental oxygen therapy and length of stay in the two groups as well as the rate of unscheduled medical visits for bronchiolitis within 72 hours. If our primary hypothesis proves correct, we may also find that significantly fewer patients in the altered saturation group will receive supplemental oxygen since many infants with mild hypoxia have only a mildly increased work of breathing which by itself would not prompt this intervention. Likewise, these patients may be discharged sooner since the physicians may not feel as obligated to observe them further “just in case”. In this scenario, we anticipate the rate of unscheduled visits would be comparable in both groups. We do not consider unscheduled medical visits to reflect safety, since many of these visits will require reassurance/education only and will not result in major management changes such as hospitalization.

3. To determine if there is a significant association between the difference in the primary outcome between the groups and the patient’s age and disease severity.

4. To determine the incremental costs/savings gained from the societal perspective in the two study groups. Economic evaluations indicate that the major societal cost associated with RSV related lower respiratory tract infections is hospitalization. If our hypothesis proves correct we would anticipate significant savings associated with determining hospitalization mainly clinically compared to the disposition dictated by variable saturation thresholds.
Background and Significance

Summarize what is already known about this child medical problem and the research gaps the project will attempt to address. Do not exceed one page. Include literature references in the Literature References page provided.

Bronchiolitis is a viral syndrome characterized by rhinorrhea, wheezing and respiratory distress, accounting for 16% of all hospitalizations in the first year of life, at a cost of 700 million US dollars. Its management is complicated by uncertainty due to lack of evidence over the optimal treatments and correlates more with local hospital or individual preferences than with disease severity. Therefore, there is a propensity to persist in practices of questionable benefit. Furthermore, the intensity of management is the main determinant of resource utilization and costs. Since the benefit of pharmacotherapy in bronchiolitis is controversial, supportive care such as oxygen therapy plays a major role. Infants with bronchiolitis undergo routine oximetry in the Emergency Department (ED), and oxygen is administered to those determined to be hypoxic. The aforementioned variation and lack of best practice consensus is relevant to when to initiate supplemental oxygen and whether or not clinical assessment should constitute the primary deciding factor with respect to disposition.

Pulse oximetry has been used since the mid 1980s and may have led to new criteria for hospitalization. Since its use became routine, the rate of hospitalization for bronchiolitis has increased by nearly 250% but mortality has remained unchanged. Concurrently, pediatric hospitalization rates for other lower respiratory tract diseases have not changed and those for other diseases have been decreasing. Although increased day care attendance may also contribute to this dramatic rise in bronchiolitis hospitalizations, several experts hypothesize that the use of frequent/continuous oximetry as well as its inconsistent interpretation with respect to when to initiate oxygen therapy may be largely responsible for this trend.

There is little evidence as to when supplemental oxygen is required, with guidelines ranging from 90%-94% without evidence delineating the associated risks and benefits. As a result, many infants with mild distress with saturations mildly diminished in the vicinity of 90% are admitted for oxygen therapy, regardless of the degree of respiratory distress, duration of desaturation, or state of wakefulness. Mild hypoxemia in bronchiolitis need not be accompanied by significantly increased work of breathing. For example, brief desaturations frequently occur after bronchodilator therapy and during sleep, without any change in the respiratory status. Oxygen saturation seems to have emerged as an overriding criterion for hospitalization from the Emergency Department (ED) and for discharge from the inpatient ward. An editorial commented that we have "…come to worship at the shrine of numbers…and that when the information is expressed in digits the truth is revealed". Prior to the adoption of oximetry, many of these admitted infants would have been discharged. Evidence suggests that previously healthy children hospitalized with bronchiolitis are unlikely to deteriorate. Among outpatients, there is no consistent evidence that a mild reduction in oxygenation predicts progression of bronchiolitis.

Only two studies have addressed the impact of oxygen saturation in bronchiolitis; one is a retrospective review and the other consists of hypothetical vignettes. The former inpatient study demonstrated that the perceived need for supplemental oxygen based on oximetry when other discharge criteria are met prolongs hospital stay in 26% of infants by an average of 1.6 days at a cost of $1500 US per hospitalization. The accompanying editorial concludes that prospective studies of the utility of oximetry should be carried out, along with a critical analysis of costs and benefits. The second study surveyed the American Academy of Pediatrics (AAP) members on their treatment preferences in bronchiolitis and found that a minimal and physiologically insignificant difference in oxygen saturation between 92% and 94% with identical respiratory rates produces a two-fold increase in intended hospitalization rates. This study illustrates that small differences in oxygen saturation have major impact on disposition.

The current devotion to oximetry and its variable interpretation have therefore created a potential for misuse. Specifically, infants with mild hypoxemia and those with brief dips in saturation during sleep who otherwise meet clinical criteria for discharge are often admitted. Hospitalizations are expensive and not without risks. Recent AAP guidelines on bronchiolitis management suggest that previously healthy children with saturation 90% or higher are unlikely to benefit from supplemental oxygen and recommend research on the most efficient use of oxygen and oxygen monitoring in this disease. However, this recommendation consists of an expert consensus based on physiological principles and has not been prospectively validated.

This is the first bronchiolitis study to examine the clinical and economic impact of making disposition decision on primarily clinical grounds, while blinding the physicians to oxygen saturations by providing them with either true saturation measurements or those which are 3 percentage points above the true values. Although physiologically insignificant and within the measurement error of the instrument, this difference has been shown to be perceived as clinically relevant and to have a major hypothetical impact on disposition, without any evidence to support this belief. We hope to find out if children with oxygen saturations above or in the vicinity of the threshold recommended for initiation of oxygen therapy by the AAP can be safely discharged based on their clinical appearance rather than to have their hospitalization dictated by a locally defined number. This study will hopefully provide much needed evidence necessary to help us interpret the oximetry results more meaningfully which may in turn lead to fewer hospitalizations, shorter length of hospital stay and lower health care costs.

Principal Investigator: Suzanne Schuh
Dr. Suzanne Schuh is a staff emergency pediatrician and a clinician investigator at the Hospital for Sick Children, with a cross-appointment as a Senior Associate Scientist in the Population Health Sciences program at the Hospital for Sick Children Research Institute. Her focus is the investigation of optimizing management of children with acute asthma, bronchiolitis and croup. Her previous studies involving numerous randomized controlled trials on these illnesses have addressed the efficacy of various aspects of pharmacotherapy such as inhaled bronchodilators and systemic corticosteroids. A paper recently published by the Journal of Pediatrics investigated the utility of chest radiographs in bronchiolitis and found that this investigation is usually not indicated since it rarely yields new useful information. The results of this paper were also introduced as a platform presentation at the annual Pediatric Academic Society meeting in San Francisco in April 2006. The proposed study constitutes a logical subsequent step in the investigation of this common disease.

A previous study by the PI of this proposal also examined the predictive value of oxygen saturation in hospitalization in acute asthma. Prior to its publication, the peer reviewers have brought up the issue of the likely bias in disposition created by the knowledge of the saturation and individual practice variation. This study should minimize this problem.

Dr. Stephen Freedman is a staff emergency paediatrician at the Hospital for Sick Children and an Associate Scientist in the Population Health Sciences program at the Hospital for Sick Children Research Institute. His research interest is optimizing management and resource utilization in children in the acute care setting, with a publication record in high impact journals such as the New England Journal of Medicine.

Dr. Allan Coates is a senior staff respirologist at the Hospital for Sick Children and a Senior Scientist at the Hospital for Sick Children Research Institute. He has both clinical expertise and an extensive publication record with respect to various aspects of management of children with acute respiratory compromise.

Dr. Patricia Parkin is a staff physician in the Division of Pediatric Medicine at the Hospital for Sick Children and an Associate Scientist in the Population Health Sciences program at the Hospital for Sick Children Research Institute. Her research concentrates on the diagnosis, prevention and treatment of common pediatric problems including acute asthma. She had also collaborated with Dr. Schuh on several trials including the aforementioned study focusing on oxygen saturation in disposition of children with acute asthma.

Dr. Upton Allen is a staff physician in the Infectious Disease Division at the Hospital for Sick Children and a Senior Associate Scientist in the Population Health Sciences program at the Hospital for Sick Children Research Institute. He has an extensive track record as a widely published senior investigator in this field, with numerous CIHR funded trials. He has also collaborated with Dr. Schuh on several previous studies, including the study of radiographs in bronchiolitis.

Dr. Andy Willan is a senior scientist with The Research Institute at the HSC with special expertise in the design and analysis of randomized controlled trials. He has more than 20 years experience as a biostatistician and a clinical trial methodologist. He will have overall responsibility for the statistical aspects of this study.

Dr. Wendy Ungar holds an appointment of a Scientist as the Hospital for Sick Children Research Institute. She is a renowned CIHR-funded health economist with special expertise in economic analysis of asthma and bronchiolitis therapy.

Zelia Da Silva is a senior respiratory technologist at our institution with expertise in the technical aspects of oxygen saturation monitoring.
Experimental Design and Methodology

Discuss in detail the design and procedures to be used to accomplish each specific aim of the project. Describe the protocols to be used, and provide a tentative sequence or timetable for the project. Include a description of facilities and other resources and the means by which you would analyze and interpret the data. If any new methodology is to be implemented, outline its expected advantage over existing methodologies. Discuss the potential difficulties and limitations of the proposed procedures and alternative approaches to achieve the aims. Point out any procedures, situations, or materials that may be hazardous to personnel and the precautions to be taken to prevent any harm. Be complete but focused in your presentation and provide sufficient detail in the narrative to allow peer reviewers to make valid judgments regarding the quality of the project proposal. Do not exceed ten (10) pages, excluding references. Include literature references in the Literature References page provided.

Primary Research Question

In previously healthy infants 6-12 weeks to 12 months of age diagnosed with acute bronchiolitis in a pediatric emergency department (ED) and monitored by hourly oximetry, is the probability of hospitalization within 72 hours of arrival in those in whose oxygen saturation display is manipulated 5 percentage points above the true measurements significantly lower compared to those whose monitors display true saturations?

Secondary Research Questions - In these two groups:

A) Is there a significant difference in the probability of supplemental oxygen administration in the ED?
B) Is there a significant difference in the length of stay in the ED?
C) Is there a significant difference in the probability of medical visits for bronchiolitis within 72 hours of commencement of the experimental intervention?
D) Is there a significant difference in the proportions of the ED physicians rating their comfort level with discharge assessed by a five point Likert scale as “very comfortable/comfortable” at 60, 120, 180, 240, 300 and 360 minutes?
E) Is there a significant association between the difference in hospitalization rate between the two groups and patient’s age, duration of symptoms, baseline saturation and clinical score?
F) What are the incremental costs/savings from the societal perspective?

Definitions

Acute Bronchiolitis

For the purposes of this study, this will consist of infants who have all of the following: coryza, cough, wheezing/ crackles and tachypnea or retractions. Only infants with their first episode of bronchiolitis will be enrolled. The probability of asthma increases with multiple wheezing episodes and this population may therefore be different from the one we wish to study.

Hospitalization

Hospitalization will include children who are admitted to the inpatient ward at the Hospital for Sick Children or transferred to another institution within 72 hours of presentation at the index visit or are treated in the ED during the initial visit for longer than 6 hours. Children staying for longer periods are usually admitted to hospital (see below under outcomes). Children successfully discharged will be those discharged within 6 hours with no subsequent inpatient admissions for bronchiolitis within 72 hours.

Unscheduled Medical Visit

This is defined as a subsequent visit of children initially discharged home, within 72 hours of presentation to any medical facility for bronchiolitis symptoms regardless of treatment received, or severity of illness.

Rationale for the difference in displayed saturations in the groups and for oxygen therapy in the study

Data identifying a single oxygen saturation as an ideal cut-off point for initiating oxygen therapy are lacking. The upper inflection point of the oxyhemoglobin dissociation curve is at an arterial oxygen pressure of 60mm Hg, which correlates with a saturation of approximately 90%. Above and to the right of this point, the curve is relatively flat and large changes in oxygen pressure result in small changes in saturation. This characteristic of the dissociation curve supports the view that previously healthy infants with bronchiolitis and saturation at or above 90% in room air at sea level are not likely to benefit from increasing partial pressure of oxygen, especially in the absence of marked respiratory distress. This reasoning led to a recent recommendation from the AAP stating that supplemental oxygen is indicated only if saturation falls persistently below 90% in infants and children. However, the necessity of giving oxygen to infants in minimal distress whose saturations diminish to the vicinity of 90% (a common scenario, especially in sleeping infants) is not known. Many mildly distressed infants experience saturations in the vicinity of 90% without any change in their respiratory status. This population may not require inpatient admission to “improve” their oximetry values. We intend to address this issue in this study. According to the bronchiolitis study by Mallory et al, a hypothetical saturation of 92% results in intended hospitalization rate of 83%, double of the hospitalization rate associated with saturation of 94%. Therefore, we have chosen a saturation difference of 3% between the groups which is within the instrument error. Since this difference corresponds to a difference in the partial pressure of oxygen of only about 8mmHg, it is also of minimal physiologic importance. The physicians will be told they can choose to administer supplemental oxygen if they feel the patients’ clinical condition requires it, regardless of oxygen saturation, or according to their interpretation of the displayed
saturation. Although some physicians like to administer supplemental oxygen when the true saturation is in the low 90s the very purpose of the study is to determine if this is indeed warranted or if children with saturations in the vicinity of 90% and higher can be successfully discharged (i.e. not admitted within 72 hours).

The hypoxemia in bronchiolitis usually arises from abnormal distribution of ventilation relative to perfusion, most likely related to viral replication and inflammation, as well as to airway reactivity and the resulting bronchospasm. Oxygen desaturations may not be associated with increasing severe distress. Inhaled salbutamol is associated with decreased saturations, usually due to a transient ventilation/perfusion mismatch or due to an increase in cardiac output with a corresponding increase in oxygen requirement.

Mild episodic hypoxia sometimes occurs in healthy infants younger than 6 months of age due to maturational changes of the individual components of respiratory function such as lung mechanics and functional residual capacity, cardio-respiratory rate, hemoglobin levels and sleep state. The propensity to desaturate is not lost until at least 130 days of life. Infants also show frequent desaturations in sleep, while in their car seats and during air travel. The British Thoracic Society suggests that desaturation to as low as 85% would have no harmful effects during airline travel. Although this population is clearly different from that with acute respiratory compromise, there is no evidence that mild acute hypoxia in bronchiolitis heralds the danger for subsequent increase in disease severity.

**Study Design**

A randomized double-blind single center trial. In order to comply with the International Committee of Medical Journal Editors, this trial will be registered with www.clinicaltrials.gov and data collection will allow for the reporting and tracking of patients in accordance with the revised CONSORT statement for parallel group randomized trials.

**Study population and setting**

Infants between 6-4 weeks and 12 months of age who present to the Emergency Department at the Hospital for Sick Children with acute bronchiolitis. The Hospital for Sick Children is a tertiary care children’s hospital in a large metropolitan city serving a catchment area of approximately five million.

**Inclusion Criteria**

1. Acute bronchiolitis defined above.
2. Age 6-4 weeks to 12 months. Children younger than 6-4 weeks of age are commonly perceived to be at higher risk of deterioration than their older counterparts. Unless the disease is clearly trivial, most infants in this age group are admitted regardless of oxygen saturation. Furthermore, in our experience most ED physicians would not be comfortable not knowing the true saturation result in extremely young infants. This age group would therefore be inappropriate to include in this study.
3. Baseline Respiratory Disease Assessment Instrument (RDAI) ≥ 3 points. Infants with no distress do not require saturation monitoring.
4. Informed consent.
5. Availability of a telephone.

**Exclusion Criteria**

1. Pre-existing pulmonary or cardiac disease, neuromuscular disease, congenital or acquired airway anomalies, hemoglobinopathies, or chronic hypoxia. These children are excluded as their underlying condition may affect their management and disposition.
2. Severe respiratory distress, defined as the retraction component on the RDAI as 8 out of 9 possible points. This population will require true saturation monitoring and including it would therefore be unethical. The RDAI, the most widely used clinical score in bronchiolitis, is reliable and has been validated. This score ranges from 0 to 17 points and assigns 8 points to wheezing and 9 to retractions. Since the extent of wheezing frequently does not correlate with the degree of distress, this parameter will not be used as an exclusion criterion. Tachypnea ≥ 70 per minute has been associated with increased risk of severe disease in some studies but not in others and will thus not be used as an exclusion criterion.
3. True baseline oxygen saturation less than 90% in room air.
4. Corrected chronological age less than 4 weeks. The exclusion criterion of prematurity will not be used. The only time prematurity matters in this study is if there is chronic lung disease (exclusion criterion). The decision to admit or discharge will remain primarily focused on the global clinical context.
5. Transfers from other institutions. These patients will have saturations documented on their transfer charts and this would bias the ED physicians’ disposition decisions.

**Sample Selection**

Children presenting when the research assistant is on duty (days and evenings) who meet the eligibility criteria will be approached for enrollment. The research assistant will keep a log of all children presenting to the ED with bronchiolitis throughout the study period whether randomized or not in order to assess the generalizability of the study. The Hospital for Sick Children is a tertiary care center, which sees the entire clinical and socio-demographic spectrum of the population. Our profile of
children with bronchiolitis should therefore be comparable to that of other institutions and the generalizability of the study should not be affected and the referral bias should be minimal. A structured data collection form will be used to assess the baseline and demographic features that may affect outcome and potentially confound the comparison. This study will require the employment of two research nurses/respiratory therapists to enroll patients on average 10 hours a day and to run the study on average 16 hours a day (8am-midnight), 5 days a week.

**Allocation**

This process will maximize the probability of the groups to be comparable with respect to unknown or unmeasured confounding variables. Following their baseline assessment and consent, the participating infants will be randomized using a permuted block randomization scheme to the **true saturation group** undergoing hourly oximetry with true saturation values and the **altered saturation group** in which the saturation measurement display is consistently 3% above the true value. Individuals will have an equal chance of allocation to either of the two study groups. An internet-based randomization service will be used (www.randomize.net). This service has been used successfully in previous trials. The randomly allocated group assignment specifying the appropriate saturation monitor code number (corresponding to either an untouched or manipulated machine, i.e. one of the two groups) will be provided on-line to the research assistant, who will receive email confirmation. The research assistant will enter the saturation monitor code number in the confidential study logbook.

**Blinding**

In this study it is necessary to blind the ED staff, the parents and the research nurse to the group assignment by concealing the true oxygen saturation values. Although the physicians will know the displayed value, they will not know whether the measurement is true or has been altered and the clinical impact on disposition should therefore be maximized. Prior to the study, the Masimo oximeters used in the altered saturation group will be manipulated by the manufacturer so that the displayed values are consistently 3% above the true values (this will be pre-tested on a group of 20 wheezing children prior to the start of the study). The research nurse will also be blinded to the group assignment in order to minimize bias in outcome assessment and in measuring other clinical parameters. The study will have two untouched and two manipulated oximeters, each with its own ID number. The oximeters for both study groups will look identical. Only the research pharmacist and the randomization service will have the key to which ID number corresponds to which oximeter (untouched versus manipulated). For safety reasons, this key will be accessible from Zeilia Da Silva or her designate if revealing this information should become necessary (extremely unlikely). To minimize the possibility of unblinding the research nurse the oximeter code assignment to the two interventions will be changed once during each bronchiolitis season and a new code list re-supplied to the randomization service and Zeilia Da Silva.

**Intervention and study procedure**

Due to the 6 hour study period, reluctance of some physicians to discharge patients after midnight and parental reluctance to participate in research during the night, we shall enroll patients between 0800 and approximately 1800 hours. A study assistant on duty will screen patients for eligibility and obtain informed consent in triage. When the PAHF research volunteers are available, they will also help pre-screen patients for eligibility and call the research nurse on the premises. All eligible infants will have their true baseline oxygen saturation measured by the research nurse which will be recorded in their ED chart only in the event of non-participation or when the study period has been concluded and disposition decided. The ED staff will only be told that the true baseline saturation is above 88% or higher but will not be told the exact number in order to minimize the impact of this knowledge on subsequent disposition. Although it can be argued that the physicians will always know at least the baseline saturation in real life, permitting its knowledge in the study would almost certainly influence the ED physicians’ clinical assessments, disposition and length of stay. The infants will then be randomized to either the true saturation group whose physicians will be presented with real saturations or the altered saturation group with saturation measurements three percentage points above true values. This difference is of minimal physiological significance but regarded by clinicians to be clinically relevant since a difference in saturation of 2% has been shown to have a potentially major impact on disposition, even though this evidence has not been proven in real practice. The ED physicians will be told that the displayed saturation may not be true and has a 50% probability of having been changed by a physiologically insignificant amount within the measurement error of the oximeter. In order to minimize the impact of any preconceived ideas regarding the significance of the 3% difference the physicians will not be told either the exact amount or the direction by which the oximeters would have been manipulated.

The research assistant will measure the respiratory rate, Respiratory Disease Assessment Instrument (RDAI) score and transcutaneous oxygen saturation at 0, 60, 120, 180, 240, 300 and 360 minutes (or at discharge time, whichever comes earlier). Oximetry of all study patients will be measured by portable oximeters which are capable of storing continuous data and graphs for up to 30 days at a set 10 second averaging time (Masimo, Irvine CA). All saturations will be measured while the infants are breathing room air for at least 2 minutes. The ED staff physician or fellow will assess all enrolled patients at these times and will estimate his/her comfort with discharge at this point, using a five point Likert scale (see outcome measures). During the study period, a concealed continuous oximetry will be done on all children in the ED to allow us to implement the safety measure of having the alarm sound when the displayed saturation drops to or below 88.25%. Since many physicians commence oxygen therapy at around 92%, we feel it important to let them know when the saturation reaches this value. Furthermore, it will be the children with saturations around 90% who will contribute the most to prolonged stays. If this occurs the research assistant will check the probe placement since probe displacement will lead to false reading and alarms. The saturation will be re-measured...
Hospitalizations occurring subsequently will be identified during the telephone follow-ups.

Since the AAP bronchiolitis guidelines approve of a therapeutic trial of inhaled bronchodilators in bronchiolitis, all enrolled children will receive 1 dose of nebulized salbutamol 2.5mg in 3ml normal saline and oxygen flow 8 liters per minute. This “therapeutic trial” will help minimize the variability in pharmacotherapy between the groups. The use of all medications administered during the study protocol will be documented in order to compare co-interventions in both study groups. At the aforementioned times the physicians in both groups will also determine whether the child can go home, their comfort with discharge (Likert scale) and their intended use of supplemental oxygen. The research assistant will record these outcomes as well as the use of other therapies and investigations necessary for the economic analysis. Since oxygen saturation is a highly changeable variable, all enrolled children will be monitored for at least 3 hours so that the ED physicians can make informed decisions based on this parameter.

At discharge, all families will receive standardized discharge instructions explaining that some respiratory distress will likely remain for another 1-2 weeks and that small frequent feeds are likely to be necessary for the next few days. These instructions will also ask the parents to return to the ED should there be an increase in the work of breathing or poor oral intake. A study coordinator will contact all families at 72 hours to inquire about any deterioration or hospitalization. All enrolled patients will be advised to visit their physicians at 24-48 hours for re-assessment.

To maximize the impact of clinical assessment on disposition, we shall:

i) Refrain from writing oximetry results on patients’ ED charts until the study is finished, i.e. the hospitalization is determined. Until then, the oximetry results will be recorded in the study record only.

ii) Standardize the phrasing of the questions by the research assistant to the ED physician regarding disposition and comfort related thereto in order to minimize the possibility of biased questioning.

iii) RDAI, respiratory rate and the physician’s intended disposition will be determined and recorded by the study assistant at each measurement time prior to the oximetry measurement.

iv) The oximetry measurement will be taken by the research assistant only. The saturation monitors mounted on the walls will be turned off and all saturation probes except the one used by the research assistant will be removed from the room.

v) The treating physicians of the discharged infants will not know the true saturation result. However, once the treating physician has decided on hospitalization, a true saturation will be measured using one of the ED oximeters (not used in the study) for the purpose of communication with the inpatient staff.

All staff in the ED will undergo education prior to the study and periodically during the study. They will be told a) the study rationale and objectives, b) that all infants participating in this study will have true baseline saturations at least 90%, c) the displayed saturation may or may not be true and may differ by a physiologically insignificant amount, d) should the displayed saturation drop below an a priori defined threshold, the measurement will be verified and if accurate the study will be discontinued and oxygen applied, e) should their patient deteriorate significantly at any time the child will be hospitalized and a true saturation will be measured, f) supplemental oxygen should be given as per clinical indication, in conjunction with the interpretation of the displayed saturation and g) that, to enable us to carry out the study, the ED monitors will not be used and only the study devices will be employed. These measures should also help alleviate the ED physicians’ fear of participation by reinforcing the safety parameters.

Unblinding Criteria

In theory, unblinding should only be used if the knowledge of the saturation is likely to/ should change management or this information is needed for communication with the inpatient staff. Prior to termination of the study, we anticipate no need for unblinding. If the child’s respiratory status deteriorates, he/she will need to be hospitalized regardless of the oxygen saturation. Once this decision has been made, the ED and in-patient staff will be told the true saturation and oxygen given as per usual practice. On the other hand, provided the child is able to self hydrate and the respiratory distress is felt to be mild enough to be compatible with discharge, revealing the saturation measurement is not justified. This will enable us to shed light on the issue if well appearing children with saturations in the vicinity of the threshold suggested by the AAP (i.e. around 90%) can be sent home.

Outcome Measures

Primary outcome measure will be the hospitalization for bronchiolitis within 72 hours of starting the study in the two groups. Hospitalization will include children who are admitted to the inpatient ward at the Hospital for Sick Children, transferred to another institution or are treated in the emergency department during the initial visit for longer than 6 hours from the start of the study. Children staying for longer periods are usually admitted to hospital. On occasion some patients who are ultimately sent home remain in the ED for a long time due to lack of inpatient beds. This population also consumes hospital resources and cannot be considered discharged. Furthermore, it would be impractical to maintain the blinding beyond 6 hours. Hospitalizations occurring subsequently will be identified during the telephone follow-ups.

and if found to be accurate the physician will be notified, supplemental oxygen will be given and the study will be discontinued.

Given the entry criteria into the study, we anticipate this occurrence extremely rarely if at all.
This outcome incorporates both the short term disposition and safety. Children going home within 6 hours who do not require subsequent hospitalization within 72 hours can be considered successfully discharged. Vast majority of patients who do require subsequent admission to hospital return within 72 hours. Hospitalizations after 72 hours are likely to be related to the progression of the disease and may have little relationship to the status at the index visit.

Unscheduled medical visits are not a good reflection of safety since most require reassurance/education only and do not result in major outcomes such as hospitalization. Although ICU admissions/ventilations for bronchiolitis do represent a major safety aspect, we do not expect this outcome to happen, given our entry criteria. However, this information will be collected (see Other outcomes below).

Hospital admission can be a very stressful event for both caregivers and infants. It also impacts on the rest of the family since caregivers often have to take time off work and arrange alternative sources of care for the other children. Hospitalization may also have a major financial impact on the family and the health care system. Economic evaluations have indicated that the major societal cost associated with RSV related lower respiratory tract infections is hospitalization[2].

Some physicians have expressed concerns regarding the remote possibility of future adverse neurobehavioral outcomes in children with history of hypoxia. The published evidence regarding potential association between hypoxia in asthma and adverse outcomes is inconsistent[3], and has not been shown to be causative. Overwhelming majority of children quoted in the literature were not previously healthy, but suffered from severe congenital heart disease or chronic sleep disorders[4] rendering them susceptible to a chronic hypoxic insult. This population was, therefore, very different from the one we want to study. We feel it unlikely that the range of mild hypoxia expected to last for a very limited time period as is the case in our study would by itself cause future adverse neurobehavioral effects. Since this long-term outcome is clearly unrealistic to examine in this study, we could not incorporate it as a measure of safety.

Secondary outcome measures - The two groups will also be compared with respect to the following:

a. The proportions of infants receiving supplemental oxygen in the ED.

b. Length of stay in the ED (from the time of arrival to the disposition decision).

c. Proportions of infants with unscheduled medical visits for bronchiolitis symptoms to any medical facility within 72 hours of the start of the study.

d. Association between the primary outcome (hospitalization) in the two groups and patients’ age, duration of respiratory distress, baseline RDAI, and baseline saturation.

e. Proportion of the ED staff/ fellows’ “strong agreement” or “agreement” with discharge at 0, 60, 120, 180, 240, 300 and 360 minutes. They will be asked the following question “Based on this infant’s clinical appearance, degree of respiratory distress, hydration status, vital signs and oxygen saturation, he/ she is ready for discharge at this point in time”:

i) Strongly agree

ii) Agree

iii) Neither agree nor disagree

iv) Disagree

v) Strongly disagree

g. The incremental costs of the true saturation group compared to the altered saturation group from the societal perspective.

Other outcomes

Admission to ICU/ventilation within 72 hours. These outcomes are extremely rare and highly unlikely to occur given our inclusion/exclusion criteria. Realistically, the study cannot be powered for a meaningful statistical analysis using this outcome. However, if it does occur, the study results will be interpreted accordingly.

Study Implementation

Prior to the study, emergency department staff physicians and fellows and emergency nurses will be educated regarding all components of the study. Particular attention will be paid to the rationale and importance of concealing the saturation and implementation of the safety measures. The research coordinator and the study assistants will also be trained in all aspects of the study execution, including obtaining informed consent, technical aspects of valid oximetry measurements and the RDAI. Also, the manipulated oximeters will be pre-tested on a cohort of 20 children with acute respiratory distress to ensure accurate 3% difference compared to the oximeters with true measurements.

This study requires the following personnel:

1. Research coordinator – this individual will supervise the research assistants, communicate with the primary investigator, organize follow-up telephone calls, oversee the budget and organize the study log of all infants 12 month of age and younger presenting with bronchiolitis to the ED within the recruitment period.
2. Research assistants – this will consist of two senior research nurses or respiratory therapists with extensive prior nursing and research experience who will be trained and responsible for screening, enrollment, study execution and use of the data collection forms.

Follow-up phone calls
All infants enrolled in the study will receive a phone call from a research coordinator approximately 72 hours after discharge from the index visit to determine subsequent medical visits or hospitalizations for bronchiolitis. If unsuccessful, calls will be made twice a day until day 7. This approach has resulted in 99% success follow-up rate in our recent bronchiolitis study. The follow-up phone calls will be made by a study coordinator who will be blinded to treatment allocation. The CIHI/OHIP/NACRS databases will also be searched to ascertain further use of health care resources within 72 hours of discharge.

Sample Size
The logs of our previous bronchiolitis studies as well as the literature suggest that approximately 30% of children with bronchiolitis are hospitalized\(^4\), or stay in the ED beyond 6 hours.

This calculation is based on the assessment of the between-group difference in proportions of hospitalizations. This is a superiority study in which the adoption of the interventional monitoring criteria can only be recommended for future practice if the rate of the primary outcome in this group is significantly lower than in the controls. The null hypothesis for the primary analysis is that the probability of hospitalization in the altered saturation arm is no less than the probability of hospitalization in the true saturation arm. That is, \(H_0: \pi_A \leq \pi_T\), where \(\pi_A\) and \(\pi_T\) are the probability of hospitalization in the altered saturation and true saturation arms, respectively. The specific alternative hypothesis for which we wish to have sufficient power is that the hospitalization rate in the altered saturation arm is lower by at least 15 percentage points, that is \(A: \pi_A \geq 0.15\). A discussion among the investigators and the ED physicians revealed that if the difference is of this magnitude adopting the interventional monitoring practice would be preferred. This target difference is also in agreement with the reported 2.5 fold increase in admission rates since routine oximetry monitoring had been adopted. For a one-sided test to have a type I error of 0.05 and a power of 80%, we need to randomize 108 patients per arm, for a total of 216\(^5\). To be conservative, we assume a refusal rate of 10% and a dropout rate of 5%. Therefore, we plan to approach 254 patients in order to randomize 228 and have complete data on 216.

Analysis

Baseline variables:
Baseline characteristics such as age, duration of respiratory distress, respiratory rate and oxygen saturation at randomization will be compared between the two groups using the appropriate descriptive statistics. Frequency counts and percentages will be given for discreet variables and means, medians, standard deviations and interquartile ranges for continuous variables. Baseline characteristics will be analyzed to determine if there is a need to adjust for any significant differences between the study groups.

The primary analysis will be performed using a one-sided Fisher’s exact test at the 5% level. A one-sided test for the primary analysis is proposed since we need only limit the probability of erroneously concluding altered saturation group has fewer hospitalizations since that would argue for deemphasizing the saturation measurements and have disposition decided on primarily clinical basis. To observe that the altered saturation group is equal or inferior to the true saturation group, whether the difference was significant or not, would argue for not changing current practice.

An intention to treat analysis will be used with all randomized participants included in the analysis as part of the groups to which they were randomized regardless of whether they completed the study or not. The rare patient for whom the hospitalization status is not known cannot be included.

The secondary analyses will include:

a) Fisher’s Exact Test will be used to compare the proportions of children receiving supplemental oxygen in the ED during the study in the two groups.

b) A Mann-Whitney U test will be used to compare treatment arms with respect to length of stay in the ED.

c) Fisher’s exact test will be used to compare the proportions of children with unscheduled medical visits within 72 hours of the index visit.

d) Fisher’s exact test will be used to compare the proportions of physicians agreeing/strongly agreeing with discharge at each time.

e) Logistic regression analysis will be used to determine association between the difference in the primary outcome while controlling for age, baseline saturation, RDAI, respiratory rate.

f) Economic analysis

The statistical tests of hypotheses for the secondary outcomes a) through g) will be set at the 0.01 level to account for the issue of multiple testing and to maintain an overall type I error of 0.05.
Economic Analysis

The objective of the economic evaluation is to assess the incremental costs/savings of using the two interventional study strategies of infants presenting with acute bronchiolitis, by examining costs and consequences. This study design will enable the capture of real world cost data, which is essential for incorporating economic evaluation into budget allocation decisions. The results will be expressed as the incremental cost (or savings) of deemphasizing pulse oximetry and making the disposition decision primarily clinically driven, provided the saturation remains within the safety limits outlined in the study. The economic evaluation will be assessed from the perspective of society, including public (provincially paid for) health care system costs, private out-of-pocket costs and parental time losses. The time horizon for the full analysis will be 72 hours in accordance with the primary study objective of examining the probability of admission.

The direct health care resource costs associated with each treatment arm consist of professional services (physicians, nurses and technologists), supplies, medications, equipment and institutional overhead costs in the ED and in the case of admitted patients, on the inpatient ward. An important cost component will be the time devoted to pulse oximetry monitoring.

Only the resource use related to the infant’s acute bronchiolitis episode within the first 72 hours will be included in the economic analysis. This includes health care provided due to the infant’s condition, due to the administration of interventions or due to adverse events related to the interventions. During the cost evaluation, prices will be assigned to each health resource item, with the exception of out-of-pocket expenses, time losses and wages which will be supplied by the parent directly. Prices will be derived from physician fee schedules, the Ontario Drug Benefits formulary, equipment wholesaler price lists and other sources. Overhead costs of ED and inpatient services and costs of resources consumed in the ED and on inpatient wards will be obtained by departmental micro-costing. Given that some costs may be incurred by the parent and some by the child, all costs will be assigned to the child as the unit of analysis. The volume of resource use and unit price of each cost item will be presented separately. This will facilitate comparisons with other studies as well as other countries. In addition, cost items will be aggregated according to the major cost categories.

The primary clinical endpoint of hospital admissions will be incorporated into the cost analysis and will therefore not be used as a surrogate marker for effectiveness. A cost consequence analysis will be undertaken that will represent the costs as well as the hospital admission rates in the true saturation group and the altered saturation group.

Sensitivity analysis will be used to test the robustness of the result to variations in the underlying assumptions. The variables that will be varied in one-way and multi-way sensitivity analyses include the outcome measure (hospitalization within 72 hours) and the most costly health resource items, e.g. Emergency Department nursing time costs and inpatient care. As some of the nursing time may be protocol driven, varying this item will allow for extrapolation of findings to non-research settings.

The impact of modifying the values of other variables, such as the prices of specific resources, may also be investigated.

Feasibility

We plan to execute the study on average 16 hours a day and to enroll new patients on average 10 hours a day, with the intervention lasting 6 hours. Bronchiolitis cases usually occur between December and April and thus we plan to recruit children during these months. Our past bronchiolitis logs indicate that approximately 500 infants with bronchiolitis present to our ED during each winter season, 400 of whom present without severe disease and with saturations ≥ 94%. Assuming that 25% will meet other exclusion criteria, 88 infants will be available for enrolment 10 hours a day 5 days a week during each winter season. A discussion among the investigators based both on experience and review of the logs of past bronchiolitis studies concluded that a brief study like this is unlikely to have a drop-out rate greater than 5%, a refusal rate greater than 10% and a miss rate greater than 5%. Approximately 76 consents and 72 patients with complete data are therefore anticipated each season. We anticipate that it will take us 51 weeks (3 bronchiolitis seasons) to accrue the necessary sample size.

Prior to writing this proposal, we have informally surveyed our ED colleagues, requesting their opinion about anticipated problems related to this issue. They appear overwhelmingly supportive. Furthermore, as mentioned in the protocol, we plan an extensive educational endeavor before and during the study, emphasizing the need for blinding the true saturations, and various safety aspects of the study.

Safety Measures –
A) Data Safety Monitoring Committee & Interim Analysis

This will consist of a biostatistician not involved in the study, a respiratory specialist and an ED attending physician. They will meet after the initial 100 patients have been enrolled in order to review the results of the interim analysis. Since this analysis is for safety purposes and no analysis of the primary or secondary outcomes will be performed, sample size adjustment and stopping rules are not required. To ensure safety of the participating subjects, there will be one planned interim analysis on the first 100 patients randomized. The interim analyses will test the hypothesis $H_0: \pi_0 \geq \pi_1 \geq 0$, versus $H_1: \pi_0 > \pi_1 < 0$ where $\pi_0$ and $\pi_1$ are the probability of hospitalization in the altered saturation and true saturation arms, respectively. That is, we are looking for evidence that the probability of hospitalization in the altered saturation arm is higher than in the true saturation arm and we will stop the trial in favour of the true saturation arm if $H_0$ is rejected at the one-sided 5% level. The interim analysis is meant to protect against the possibility that altered saturations (i.e. deemphasizing saturation measurements) produces more hospitalizations. Since $H_0$ and $H_1: \pi_0 \geq \pi_1 \leq 0$ (the null hypothesis for the final analysis) are different hypotheses, testing $H_1$ will
not increase the probability of rejecting $H_0$ erroneously, that is, testing $H_1$ will not increase the type I error associated with the final analysis.

In addition to the interim analysis, the Data Safety Monitoring Committee will meet once during each bronchiolitis season to discuss any significant concerns raised by the investigators and the research coordinators. Furthermore, their will be ad hoc meetings should any cases of ICU admissions or ventilation within 72 hours arise. The DSMC will review these cases in detail and decide if any action needs to be taken. The PI will contact the DSMC within 48 hours of obtaining information of all emergency unblindings (see also Adverse events).

B) Adverse Events & Safety of the participants
The precise oxygen saturation associated with acute respiratory compromise which results in adverse effects is not known. However, this point lies well below the range of saturations which will occur in our study. The degree of hypoxia which will happen in our patient population can be expected to result in no adverse effects. High risk population such as infants with low cardiac output, sepsis or other system derangement necessitating normal oxygen saturation will be excluded. Children with chronic hypoxia which may result in pulmonary hypertension will not participate either.

In this study, to maximize the safety of the participants, infants with saturations $<90\%$ and those in severe respiratory distress at presentation will be excluded. This will minimize the probability of subsequent significant desaturations and/or major deterioration. All enrolled infants will be monitored hourly by both the research nurse and the ED physicians. Should the status of any patient deteriorate significantly, he/she will be admitted and appropriate therapy instituted. Safety alarms are not normally used during intermittent oximetry. However, as an additional safety measure we have instituted continuous oximetry monitoring with a safety alarm to sound should the displayed saturation drop below $88\%$. Additionally, should the true saturation drop below $87\%$, the alarm will sound and appropriate measures instituted. The oxygen saturation threshold for study entry and for commencing supplemental oxygen is in close proximity to that quoted in the recently published AAP guidelines on bronchiolitis management.

The main adverse events which will be documented and reported in the manuscript will be the children requiring ventilation and those requiring ICU care within 72 hours of the initial discharge. These events will also be considered serious, mandating their reporting to the Research Ethics Board within 48 hours.

Divisional support for the study
This study demands extensive ongoing education of the ED physicians and nurses in the necessity of the binding of the true oxygen saturations, implementation and maintenance of the blinding strategies as well as our goal to use oximetry efficiently and interpret its results appropriately. For some staff who currently place great importance on oximetry this study will represent a significant departure from usual practice. Dr. William Mounstephen, our Divisional Director and Dr. Bruce Minnes, our Associate Clinical Director, both support the importance of this study and are prepared to assist with its implementation.

Dissemination of Results and Future Directions
The results of this study will be submitted for presentation at either the annual meeting of the Pediatric Academic Society, the Society for Academic Emergency Medicine or the American Academy of Pediatrics. We shall also submit the manuscript for publication in a peer reviewed scientific journal. Future studies will need to address the impact of oximetry on the hospitalized patients with bronchiolitis.

Limitations
It is possible that not knowing the true saturation may make the ED physicians more cautious than usual and that more patients may be admitted as a result. However, this is equally likely to occur in both study arms and should not contribute to the difference in primary outcome between the groups.

Since the research nurse will measure the true screening saturations it is possible that he/she may become unblended upon subsequently using the study oximeters. However, this probability is not large since saturations frequently vary by several percent over a period of several minutes that it will take the nurse to start the study.

It is quite likely that the number of patients with true saturations below $90\%$ will be relatively small and the power to make firm conclusions about the probability of successful discharge at each saturation level below this threshold may be limited.

The question of the impact of oximetry on inpatient stay has been retrospectively explored, and needs to be investigated prospectively in a separate study.
Literature References

36. Lenard HG. The development of sleep spindles in the EEG during the first two years of life. Neuropadiatrie 1970;1(3):264-76.
Collaborative Arrangements

Provide a detailed explanation of any project-related programmatic, financial, and administrative arrangements made between the Supervising Institution and any collaborating organizations. Furnish letters confirming the agreement between the Supervising Institution and any collaborating organization.

None required.
Principal Investigator: Suzanne Schuh

International Activities

If the project will be conducted outside the United States at any time, you must give a complete explanation of international involvement. Document and include project endorsements by foreign governments if any are required in the setting in which the work is being carried out.

All project activity will occur at the Hospital for Sick Children, Toronto, ON, Canada since this is the institutional affiliation of all investigators related to this project. No foreign government endorsement is required for this project.
## Detailed Budget for First 12-Month Budget Period

### Personnel

<table>
<thead>
<tr>
<th>Name</th>
<th>Project position title</th>
<th>%</th>
<th>Hours per week</th>
<th>Salary</th>
<th>Fringe benefits</th>
<th>Salary + Fringe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suzanne Schuh</td>
<td>Principal Investigator</td>
<td>20</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Stephen Freedman, Allan Coates,</td>
<td>Co-Investigators</td>
<td>2</td>
<td>1 each</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Patricia Parkin, Upton Allen,</td>
<td></td>
<td></td>
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<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Andrew Willan, Wendy Ungar,</td>
<td></td>
<td></td>
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<td>0</td>
<td>0</td>
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</tr>
<tr>
<td>Zelia DaSilva</td>
<td></td>
<td></td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
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<tr>
<td>Biljana Klasninovska</td>
<td>Data Management</td>
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</table>

**Subtotal of personnel costs** 77779

### Consultant(s) Costs

<table>
<thead>
<tr>
<th>Name</th>
<th>Institutional affiliation</th>
<th>Salary</th>
<th>Fringe benefits</th>
<th>Salary + Fringe</th>
</tr>
</thead>
</table>

**Subtotal of consultant costs**

### Supplies (itemize, expand any boxes as needed)

- Paper
- Photocopying
- File Folders
- Binders

**Supplies (continued)**

**Subtotal** = 900

### Domestic travel (itemize)

**Domestic travel (continued)**

**Subtotal**

### Foreign travel (itemize)

**Foreign travel (continued)**

**Subtotal**

### Patient care costs (itemize)

**Patient care costs (continued)**

**Subtotal**

### Other expenses (itemize)

- Technical aspects of blinding
- Internet Randomization Service

**Other expenses (continued)**

**Subtotal** = 2250

### Indirect costs-Supervising Institution (not to exceed 7 percent of the above subtotals)

**Subtotal** = 5665

### Equipment (itemize)

- 4 Oximeters (Masimo)
- Technical costs for blinding oximeters
- 240 probes

**Equipment (continued)**

**Subtotal** = 19250

**Contractual Costs (itemize on the following page, and enter the total as the subtotal on this line.**

**Subtotal**

**Total First Year Budget** = 105844
Principal Investigator: Suzanne Schuh

**Contractual Costs for First 12-Month Budget Period**

(Limit to one page)

<table>
<thead>
<tr>
<th>Personnel</th>
<th>Time/Effort</th>
<th>US $ Amount Requested (Omit cents)</th>
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</thead>
<tbody>
<tr>
<td>Name</td>
<td>Project position title</td>
<td>%</td>
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Subtotal of personnel costs: 0

**Consultant(s) Costs**

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<tr>
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<th>Fringe benefits</th>
<th>Salary + Fringe</th>
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Subtotal of consultant costs: 0

**Supplies** (itemize, expand any boxes as needed)

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<th>Supplies (itemize, expand any boxes as needed)</th>
<th>Supplies (continued)</th>
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Subtotal: 0

**Domestic travel** (itemize)

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Subtotal: 0

**Foreign travel** (itemize)

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Subtotal: 0

**Patient care costs** (itemize)

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<th>Patient care costs (itemize)</th>
<th>Patient care costs (continued)</th>
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Subtotal: 0

**Other expenses** (itemize)

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</tbody>
</table>

Subtotal: 0

**Indirect costs-Contractual Institution**

(not to exceed 7 percent of the above subtotals)

<table>
<thead>
<tr>
<th>Indirect costs-Contractual Institution</th>
<th>Indirect costs-Contractual Institution</th>
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</table>

Subtotal: 0

**Equipment** (itemize)

<table>
<thead>
<tr>
<th>Equipment (itemize)</th>
<th>Equipment (continued)</th>
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<tbody>
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</tbody>
</table>

Subtotal: 0

(Enter this total as the first year contractual costs Subtotal on the Detailed Budget for First 12-Month Budget page) Total: 0
### Principal Investigator: Suzanne Schuh

**Detailed Budget for Second 12-Month Budget Period** (Expand the cells in the itemized sections as necessary, but limit total space to one page)

#### Personnel

<table>
<thead>
<tr>
<th>Name</th>
<th>Project position title</th>
<th>Time/Effort</th>
<th>US $ Amount Requested (Omit cents)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suzanne Schuh</td>
<td>Principal Investigator</td>
<td>20/8/0</td>
<td>0/0/0</td>
</tr>
<tr>
<td>Stephen Freedman</td>
<td>Co-Investigators</td>
<td>2 each/1 each/0</td>
<td>0/0/0</td>
</tr>
<tr>
<td>Allan Coates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patricia Parkin</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Upton Allen</td>
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<td></td>
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<tr>
<td>Andrew Willan</td>
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<tr>
<td>Wendy Ungar</td>
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<tr>
<td>Zelia DaSilva</td>
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</tbody>
</table>

#### Consultant(s) Costs

<table>
<thead>
<tr>
<th>Name</th>
<th>Institutional affiliation</th>
<th>Salary</th>
<th>Fringe benefits</th>
<th>Salary + Fringe</th>
</tr>
</thead>
</table>

#### Supplies (itemize, expand any boxes as needed)

<table>
<thead>
<tr>
<th>Supplies (continued)</th>
</tr>
</thead>
</table>

#### Domestic travel (itemize)

<table>
<thead>
<tr>
<th>Domestic travel (continued)</th>
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</thead>
</table>

#### Foreign travel (itemize)

<table>
<thead>
<tr>
<th>Foreign travel (continued)</th>
</tr>
</thead>
</table>

#### Patient care costs (itemize)

<table>
<thead>
<tr>
<th>Patient care costs (continued)</th>
</tr>
</thead>
</table>

#### Other expenses (itemize)

<table>
<thead>
<tr>
<th>Other expenses (continued)</th>
</tr>
</thead>
</table>

#### Indirect costs-Supervising Institution (not to exceed 7 percent of the above subtotals)

<table>
<thead>
<tr>
<th>Indirect costs-Supervising Institution</th>
</tr>
</thead>
</table>

#### Equipment (itemize)

<table>
<thead>
<tr>
<th>Equipment (continued)</th>
</tr>
</thead>
</table>

#### Contractual Costs (Itemize on the following page, and enter the total as the subtotal on this line.)

<table>
<thead>
<tr>
<th>Contractual Costs</th>
</tr>
</thead>
</table>

#### Total Second Year Budget

<table>
<thead>
<tr>
<th>Total Second Year Budget</th>
</tr>
</thead>
</table>
**Contractual Costs for Second 12-Month Budget Period** (Limit to one page)

<table>
<thead>
<tr>
<th>Personnel</th>
<th>Time/Effort</th>
<th>US $ Amount Requested (Omit cents)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Name</strong></td>
<td><strong>Project position title</strong></td>
<td><strong>%</strong></td>
</tr>
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<td></td>
</tr>
<tr>
<td>Subtotal of personnel costs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Consultant(s) Costs**

<table>
<thead>
<tr>
<th>Name</th>
<th>Institutional affiliation</th>
<th>Salary</th>
<th>Fringe benefits</th>
<th>Salary + Fringe</th>
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<tbody>
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<tr>
<td>Subtotal of consultant costs</td>
<td></td>
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</table>

**Supplies (Itemize)**

<table>
<thead>
<tr>
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<th>Subtotal</th>
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<tbody>
<tr>
<td></td>
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</tr>
<tr>
<td>Domestic travel</td>
<td>Domestic travel (continued)</td>
<td>Subtotal</td>
</tr>
<tr>
<td>Foreign travel</td>
<td>Foreign travel (continued)</td>
<td>Subtotal</td>
</tr>
<tr>
<td>Patient care costs</td>
<td>Patient care costs (continued)</td>
<td>Subtotal</td>
</tr>
<tr>
<td>Other expenses</td>
<td>Other expenses (continued)</td>
<td>Subtotal</td>
</tr>
<tr>
<td>Indirect costs-Contractual Institution (not to exceed 7 percent of the above subtotals)</td>
<td>Subtotal</td>
<td></td>
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</tbody>
</table>

**Equipment (Itemize)**

<table>
<thead>
<tr>
<th>Equipment (Itemize)</th>
<th>Equipment (continued)</th>
<th>Subtotal</th>
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<tbody>
<tr>
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</tbody>
</table>

(Enter this total as the second year contractual costs Subtotal on the Detailed Budget for Second 12-Month Budget page)

Total = 0
### Personnel

<table>
<thead>
<tr>
<th>Name</th>
<th>Project position title</th>
<th>Time/Effort</th>
<th>US $ Amount Requested (Omit cents)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suzanne Schuh</td>
<td>Principal Investigator</td>
<td>20 % 8 hours per week</td>
<td>Salary 0 Fringe 0 Salary + Fringe 0</td>
</tr>
<tr>
<td>Stephen Freedman, Allan Coates, Patricia Parkin, Upton Allen, Andrew Willan, Wendy Ungar, Zelia DaSilva</td>
<td>Co-Investigators 2 each 1 each</td>
<td>0 0</td>
<td>0 0</td>
</tr>
<tr>
<td>Research Coordinator</td>
<td></td>
<td>25 % 10 hours per week</td>
<td>8464 1947 10411</td>
</tr>
<tr>
<td>Research Assistant</td>
<td></td>
<td>100 % 37.5 hours per week</td>
<td>28935 6655 35590</td>
</tr>
<tr>
<td>Research Assistant</td>
<td></td>
<td>100 % 37.5 hours per week</td>
<td>28935 6655 35590</td>
</tr>
</tbody>
</table>

**Subtotal of personnel costs:** 81591

### Consultant(s) Costs

<table>
<thead>
<tr>
<th>Name</th>
<th>Institutional affiliation</th>
<th>US $ Amount Requested (Omit cents)</th>
</tr>
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</table>

**Subtotal of consultant costs:** 0

### Supplies (itemize, expand any boxes as needed)

<table>
<thead>
<tr>
<th>Supplies (continued)</th>
</tr>
</thead>
</table>

**Subtotal:**

### Domestic travel (itemize)

<table>
<thead>
<tr>
<th>Domestic travel (continued)</th>
</tr>
</thead>
</table>

**Subtotal:**

### Foreign travel (itemize)

<table>
<thead>
<tr>
<th>Foreign travel (continued)</th>
</tr>
</thead>
</table>

**Subtotal:** 1700

### Patient care costs (itemize)

<table>
<thead>
<tr>
<th>Patient care costs (continued)</th>
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</thead>
</table>

**Subtotal:**

### Other expenses (itemize)

<table>
<thead>
<tr>
<th>Other expenses (continued)</th>
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</thead>
</table>

**Subtotal:** 11622

### Indirect costs-Supervising Institution (not to exceed 7 percent of the above subtotals)

**Subtotal:** 6644

### Equipment (itemize)

<table>
<thead>
<tr>
<th>Equipment (continued)</th>
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</table>

**Subtotal:**

### Contractual Costs (Itemize on the following page, and enter the total as the subtotal on this line.)

**Subtotal:**

**Total Third Year Budget:** 101557
**Principal Investigator:** Suzanne Schuh

### Contractual Costs for Third 12-Month Budget Period (Limit to one page)

<table>
<thead>
<tr>
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<th>Time/Effort</th>
<th>US $ Amount Requested (Omit cents)</th>
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<tbody>
<tr>
<td>Name</td>
<td>Project position title</td>
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**Subtotal of personnel costs**

0

### Consultant(s) Costs

<table>
<thead>
<tr>
<th>Consultant(s)</th>
<th>Institutional affiliation</th>
<th>Salary</th>
<th>Fringe benefits</th>
<th>Salary + Fringe</th>
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**Subtotal of consultant costs**

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### Supplies (itemize, expand any boxes as needed)

<table>
<thead>
<tr>
<th>Supplies (continued)</th>
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**Subtotal**

0

### Domestic travel (itemize)

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<tr>
<th>Domestic travel (continued)</th>
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**Subtotal**

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### Foreign travel (itemize)

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<th>Foreign travel (continued)</th>
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**Subtotal**

0

### Patient care costs (itemize)

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<th>Patient care costs (continued)</th>
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</table>

**Subtotal**

0

### Other expenses (itemize)

<table>
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<th>Other expenses (continued)</th>
</tr>
</thead>
</table>

**Subtotal**

0

### Indirect costs-Contractual Institution (not to exceed 7 percent of the above subtotals)

**Subtotal**

0

### Equipment (itemize)

<table>
<thead>
<tr>
<th>Equipment (continued)</th>
</tr>
</thead>
</table>

**Subtotal**

0

*(Enter this total as the third year contractual costs Subtotal on the Detailed Budget for Third 12-Month Budget page)*  **Total**

0
Justification for the budget:

Investigators
The study investigators do not require any salary support.

Clinical Research Coordinator
This individual will be a senior nurse/ respiratory therapist who will be responsible for the following:
1. Communication with research assistants, scheduling and organizing payroll.
2. Promoting the study within the emergency department, telephone follow-ups.
3. Liaison with principle investigator regarding any study concerns.
5. Study log of all patients with bronchiolitis presenting to the ED and those who were not enrolled due to absence from duty, due to exclusion criteria, refusal to participate and missed patients.
6. Data abstraction into the database, dissemination of the results, participation in manuscript preparation.

Research Nurse/ Respiratory Therapist
This study requires hiring two full-time research assistants who will be trained by the principal investigator and involved in eligibility assessment, patient enrollment, randomization, use of patient data form, patient monitoring and outcome data assessment during the study, as well as ensuring that the ED staff looking after patients is blinded to true oxygen saturations. Since they will also measure the clinical score, vital signs, and have to recognize any changes in the respiratory status in a timely fashion, these individuals will be senior pediatric research nurses with previous nursing and research experience. Our extensive experience confirms the absolute
necessity for a dedicated research assistant present on the premises. The busy ED staff cannot be expected to contact the research nurse in a timely fashion and any recruitment relying on calling a nurse on call would therefore compromise enrollment.

Since the interventional period will last approximately 6 hours, we shall enroll patients from 8 AM to 6 PM and execute the study until approximately midnight. The bronchiolitis season extends from early December through April and the study will therefore run for 21 weeks during each winter season. The salary for the research assistants (nurses) will be $34.30 US per hour plus 23% fringe benefits (mandated by the institution) and will increase 3.5% per year thereafter. This rate is based on the hourly rate of a senior nurse working in the Hospital for Sick Children. We anticipate the study will require enrollment during three 21-week winter seasons for a total of 63 weeks of employment.

Database Development
Consultation with the Hospital for Sick Children Research Institute database development staff provided an estimate of 40 hours required at a rate of $33.10 US per hour plus 23% fringe benefits.

Internet Randomization Service
A standard fee for this service is $2500 Canadian or approximately $2250 US dollars.

Statistical Analysis
This study will require an extensive statistical analysis. Dr. Andy Willan will closely supervise his statistical staff. He estimates this process will require 100 hours at a standard fee of $50.00 Canadian an hour ($45.00 US) plus 23% fringe benefits.

Economic Analysis
This study will require an extensive statistical analysis. Dr. Wendy Ungar will closely supervise her staff to complete this task. She estimates this process will require 100 hours at a standard fee of $50.00 Canadian an hour ($45.00 US) plus 23% fringe benefits.

Equipment
Since we anticipate enrolling more than one child at the same time, we intend to purchase 4 portable oximeters, at a cost of $3150US each. This price is directly quoted from the manufacturer. To manipulate two oximeters for blinding purposes will cost approximately $1275US per monitor. We also need to buy 240 oximeter probes at a cost of $17US per probe.

Travel
The results of this study will be submitted for presentation at a scientific meeting and a budget to cover the cost of the conference is therefore requested.

Publication Costs
The fee for reprints of the published manuscript is included in this budget.
Principal Investigator: Suzanne Schuh

Other Support
For each of the professionals named on the budget pages, list the title, start and end dates; source of funding; and yearly amounts of all state, federal, commercial, and private funding support. Include this information for active grants, proposals under review, and proposals being prepared for submission. Indicate the percentage of effort for investigators in each project.

Suzanne Schuh, MD, FRCP(C), FAAP (PEM)
Staff Pediatrician and Research Director, Emergency Department
Senior Associate Scientist, Research Institute
The Hospital for Sick Children
Professor of Pediatrics, University of Toronto
Start Date: January 1, 1985
End Date: None
Source of funding: PSI, HSC Foundation, Merck Frosst Canada, Trudell Medical
Annual state/federal/commercial/private support: None

Current Support for this Study:
Impact of Oximetry on Hospitalization in Acute Bronchiolitis.
Funded by Physicians’ Services Incorporated Foundation March 2007 for $163,000 CND

Active grants:
1. Emergency Department Rapid Intravenous Rehydration (RIVR) for Pediatric Gastroenteritis: A Randomized Controlled Trial
   Physicians’ Services Incorporated ($165,000 2006 - 2008)
   Percentage of Effort: 10% involvement

2. Predictors for Diagnostically Accurate Ultrasound in Children with Suspected Appendicitis.
   HSC Foundation ($128,000 2007 - 2009)
   Percentage of Effort: 20% involvement

3. Can Montelukast Shorten Corticosteroid Therapy in Children with Mild to Moderate Acute Asthma?
   Merck Frosst Canada ($314,414 2005 - 2007)
   Percentage of Effort: 30% involvement

4. Funding for research Coordinator Initiative spearheaded by S. Schuh, the Research Director in the ED.
   Trudell Medical ($50,000 2006 - 2008)
   Percentage of Effort: 5% involvement

Proposals under review:
1. Can Young Infants with Acute Wheezing be Stabilized With Salbutamol By Metered Dose Inhalers?
   Submitted to HSC Foundation October 2006
   Percentage of Effort on grant: 80% involvement

2. Efficacy of Cold Air in the Treatment of Croup.
   Submitted to Physicians’ Services Incorporated Foundation February 2007
   Percentage of Effort on grant: 30% involvement

   Submitted to Physicians’ Services Incorporated Foundation November 2006
   Percentage of Effort on grant: 10% involvement

   Submitted to HSC Foundation October 2006
   Percentage of Effort on grant: 10% involvement

Proposals being prepared for submission: None

Stephen B. Freedman, MD, MSCI, FAAP, FRCPC
Staff Pediatrician, Emergency Department
The Hospital for Sick Children
Assistant Professor of Pediatrics, University of Toronto  
Start Date: October 15, 2004  
End Date: None  
Source of funding: Pediatric Consultants & Physician’s Services Incorporated  
Annual state/federal/commercial/private support: None  
Active grants:  
1. The Impact of an Emergency Department and Community Based Gastroenteritis Protocol on Knowledge and Emergency Department Utilization.  
   Pediatric Consultants Educational Research Grant ($4,527 2005)  
   Percentage of Effort: 80% involvement  
2. Emergency Department Rapid Intravenous Rehydration for Pediatric Gastroenteritis: A Randomized Controlled Trial.  
   Physician Services Incorporated Foundation ($156,000 2005 - 2007)  
   Percentage of Effort: 80% involvement  
Proposals under review:  
1. Isotonic versus hypotonic IV maintenance fluids in children: a randomized controlled trial.  
   Submitted to Paediatric Consultants Creative Professional Activity Grant March 2007  
   Percent of effort on Grant: 20%  
Proposals being prepared for submission:  
1. The role of Probiotics in Gastroenteritis in a Pediatric Emergency Department

Allan Coates, MD, CM  
Staff Physician  
Division of Respiratory Medicine  
The Hospital for Sick Children  
Professor of Pediatrics, University of Toronto  
Start Date: January 1, 1997  
End Date: None  
Source of funding: Canadian Cystic Fibrosis Foundation & CIHR  
Annual state/federal/commercial/private support: None  
Active grants:  
1. The impact of habitual physical activity on disease progression in cystic fibrosis.  
   Canadian Cystic Fibrosis Foundation (2003-2006 $232,923; 2006-2008 $180,000)  
   Percentage of Effort: 20% involvement  
2. Training Program in Clinical Nutrition  
   Canadian Institutes of Health Research (CIHR) Grant (2002-2008 $1,590,000)  
   Percentage of Effort: 10% involvement  
Proposals under review: None  
Proposals being prepared for submission: None

Patricia Parkin, MD, FRCP(C)  
Staff Physician  
Division of Pediatric Medicine  
The Hospital for Sick Children  
Assistant Professor of Pediatrics, University of Toronto  
Start Date: July 1, 1988  
End Date: None  
Source of funding: University of Toronto, Hospital for Sick Children Foundation, Dunone Institute, PSI, Sanofi, Heart and Stroke Foundation,  
Annual state/federal/commercial/private support: None  
Active grants:  
1. Treatment choices for children with typical acute immune thrombocytopenic purpura: development of a decision aid University of Toronto (2006-2011 $10,000)  
   Percentage of Effort: 50%  
2. Palindromy at the NF1 locus as a risk factor for NF1-associated malignancy  
   Hospital for Sick Children (2006-2009 $45,023)  
   Percentage of Effort: 50%
3. Nutritional education and the prevention of iron depletion in children 9 months to 2 years: a randomized trial
   Danone Institute (2006-2008 $61,148)
   Percentage of Effort: 70%

4. Emergency Department rapid intravenous rehydration for pediatric gastroenteritis: a randomized controlled trial
   Physicians Services Incorporated Foundation (2006-2008 $156,000)
   Percentage of Effort: 10%

5. Does the order in which vaccines are administered affect pain response? A randomized, double-blind, clinical trial of
   Pentacel vs Prevnar
   Sanofi (2006-2007 $17,270)
   Percentage of Effort: 10%

6. An office based intervention to improve media use in preschool children: a randomized controlled trial
   Hospital for Sick Children (2006-2007 $9,975)
   Percentage of Effort: 30%

7. Modifiable risk factors for acute chest syndrome in children with sickle cell disease admitted to hospital with a painful
   crisis
   Hospital for Sick Children (2005-2007 $3,750)
   Percentage of Effort: 30%

8. PEWS translation project: from retrospective algorithm to real-time bedside tool
   Heart and Stroke Foundation (2006-2007 $74,652)
   Percentage of Effort: 10%

Proposals under review: None
Proposals being prepared for submission: None
Canadian Institute of Health Research (2005-2012 $3,585,161)  
*Percentage of Effort: 5% involvement*

2. **The Twin Birth Study**  
Canadian Institute of Health Research (2003-2011 $8,608,045)  
*Percentage of Effort: 5% involvement*

3. **Translating research on pain in children**  
Canadian Institute of Health Research (2006-2011 $5,928,858)  
*Percentage of Effort: 5% involvement*

4. **Development of statistical methodology in cost-effectiveness analysis**  
Natural Sciences and Engineering Research Council of Canada (2003-2008 $44,000)  
*Percentage of Effort: 70% involvement*

5. **Emergency Department Rapid Intravenous Rehydration for Pediatric Gastroenteritis: A Randomized Controlled Trial**  
Physicians Services Incorporated Foundation (2006-2007 $156,000)  
*Percentage of Effort: 5% involvement*

6. **Early External Cephalic Version 2-Trial**  
Canadian Institute of Health Research (2003-2007 $2,853,717)  
*Percentage of Effort: 5% involvement*

7. **SELAN (Structured Early Labour Assessment and Care)**  
Canadian Institute of Health Research (2003-2007 $665,668)  
*Percentage of Effort: 5% involvement*

**Proposals under review: None**  
**Proposals being prepared for submission: None**

**Wendy Ungar, M. Sc, PhD**  
Senior Scientist, Child Health Evaluative Sciences  
The Hospital for Sick Children  
Associate Professor, Department of Health Policy, Management and Evaluation,  
Faculty of Medicine, University of Toronto  
Start Date: March 1999  
End Date: None  
Source of funding: CIHR, AllerGen NCE, Organization of Teratology Information Services  
Annual state/federal/commercial/private support: None  
Active grants:  
1. **An economic evaluation of teratology information services (TIS)**  
Organization for Teratology Information Services (2006-2008 $50,000 US)  
*Percentage of Effort: 10%*

2. **Costs incurred by families of children newly diagnosed with cancer**  
National Cancer Institute of Canada (2006-2008 $356,822)  
*Percentage of Effort: 2.5%*

3. **The Ulysses Program: Building Research Capacity in Health Technology Assessment and Management**  
Canadian Coordinating Office for Health Technology Assessment (2006-2007 $99,728)  
*Percentage of Effort: 10%*

4. **Costs Incurred by Families of Children Newly Diagnosed with Cancer**  
Paediatric Oncology Group of Ontario (2006-2008 $55,000)  
*Percentage of Effort: 2.5%*

5. **Financial barriers to medication use in children with asthma: effect on health outcome**  
AllerGen National Centre for Excellence (2005-2007 $100,000)  
*Percentage of Effort: 25%*

Decision-Making
The Canadian Institutes of Health Research (2004-2007 $224,726)
Percentage of Effort: 25%

7. The Pediatric Economic Database Evaluation (PEDE) Project
Percentage of Effort: 2%

8. Pharmaceutical cost-sharing and health outcomes in children with asthma
The Canadian Institutes of Health Research and Hospital for Sick Children Research Institute New Investigator Career Award
(2002-2007 $250,000)
Percentage of Effort:

9. Fetal Alcohol Syndrome: Oxidative Stress and Innovative Therapies
Canadian Institutes of Health Research New Emerging Team (2002-2007 $1,250,000)
Percentage of Effort: 1%

Proposals under review:

1. Management proposal for CADTH’s partners in health technology assessment
Submitted to Canadian Agency for Drugs and Technologies in Health December 2006
Percentage of Effort:

2. Young infants with acute recurrent wheezing - to puff or not to puff? A randomized controlled trial
Submitted to Hospital for Sick Children Foundation October 2006
Percentage of Effort:

3. Antidepressants and Risk of Suicide or Self-harm in Canadian Youth: A national population-based study.
Submitted to The Canadian Institutes of Health Research September 2006
Percentage of Effort:

Zelia Da Silva, RT
Respiratory Technologist, Division of Respiratory Medicine
The Hospital for Sick Children
Start Date: 1993
End Date: None
Source of funding: None
Annual state/federal/commercial/private support: None
Active grants: None
Proposals under review: None
Proposals being prepared for submission:
Collaborator: Efficacy of Cold Air in the Treatment of Croup
Percentage of Effort: 5%
Biographical Sketch

Give the following information for key personnel, beginning with the principal investigator.

Name: Suzanne Schuh

Title: Staff Pediatrician and Research Director, Emergency Department
The Hospital for Sick Children
Senior Associate Scientist, Research Institute
Professor of Pediatrics, University of Toronto

Education

Begin with baccalaureate or other initial professional education, and include all postdoctoral training.

<table>
<thead>
<tr>
<th>Institution and location</th>
<th>Degree</th>
<th>Year</th>
<th>Field of study</th>
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<tbody>
<tr>
<td>The University of Toronto</td>
<td>B.Sc.</td>
<td>1973</td>
<td>Science</td>
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<tr>
<td>Toronto, Ontario</td>
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<tr>
<td>The University of Toronto</td>
<td>M.D. (Honours)</td>
<td>1977</td>
<td>Medicine</td>
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<td>Toronto, Ontario</td>
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<tr>
<td>The American Board of Pediatrics</td>
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<td>1981</td>
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<tr>
<td>The University of Toronto</td>
<td>FRCP(C)</td>
<td>1981</td>
<td>Pediatrics</td>
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<td>Toronto, Ontario</td>
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</tr>
</tbody>
</table>

Research or Professional Experience

Concluding with your present position, list in chronological order all previous employment, experience, and honors. List in chronological order complete references to all publications during the past three years and to representative earlier publications pertinent to this application.

Previous Employment:

1982 - 1984 Consultant paediatric practice, Oshawa Clinic, Oshawa, Ontario

1983 - 1984 Part-time staff Emergency Department and General Paediatrics, The Hospital for Sick Children, Toronto, Ontario

1985 - Present Full-time Staff Emergency Department, The Hospital for Sick Children, Toronto, Ontario

1992 - 2000 Paediatric Emergency Fellowship Director, The Hospital for Sick Children, Toronto, Ontario

1998 - 2005 Associate Scientist, Research Institute, The Hospital for Sick Children, Toronto, Ontario

2000 - Present Emergency Research Director, The Hospital for Sick Children, Toronto, Ontario

2005 - Present Senior Associate Scientist, Research Institute, The Hospital for Sick Children, Toronto, Ontario

Honours:

Paediatric Trainee Research Award for Best Subspecialty Poster, Research Institute, The Hospital for Sick Children. Does Oximetry Predict Length of Therapy in Children with Acute Asthma? 2003

Best Research Design - University of Toronto Emergency Medicine Award Does Oximetry predict length of therapy in children with acute asthma. 2003

University of Toronto Faculty of Medicine Physician Research Award for Career Excellence. Nominated for this award. February 2007

Publications:


To insert another biographical sketch, make sure macros are enabled, and then press the ALT and 1 keys (ALT + 1). For instructions on enabling macros, see: http://office.microsoft.com/assistance/2002/articles/pwMacroSecurity.aspx
Principal Investigator: Suzanne Schuh

Biographical Sketch  Do not exceed two pages per biographical sketch.

Give the following information for key personnel, beginning with the principal investigator.

Name: Stephen Freedman

Title: Staff Pediatrician, Emergency Dept.
The Hospital for Sick Children
Assistant Professor of Pediatrics
University of Toronto

Education Begin with baccalaureate or other initial professional education, and include all postdoctoral training.

<table>
<thead>
<tr>
<th>Institution and location</th>
<th>Degree</th>
<th>Year</th>
<th>Field of study</th>
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<tr>
<td>McGill University</td>
<td>Medicine Preparatory Year</td>
<td>1992</td>
<td>Pre-medicine</td>
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<td>Montreal, Quebec</td>
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<tr>
<td>McGill University</td>
<td>MDCM</td>
<td>1996</td>
<td>Medicine</td>
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<td>Montreal, Quebec</td>
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<tr>
<td>Northwestern University</td>
<td>MSCI</td>
<td>2003</td>
<td>Master Degree in Clinical Investigation</td>
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<td>Chicago, Illinois</td>
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Research or Professional Experience

Concluding with your present position, list in chronological order all previous employment, experience, and honors. List in chronological order complete references to all publications during the past three years and to representative earlier publications pertinent to this application.

Previous Employment:

2000 - 2001 Associate Staff, The Hospital for Sick Children, Toronto, Ontario

2002 - 2004 Affiliate, Division of General Medicine, Children's Memorial Hospital, Chicago, IL.

2003 - 2004 Provisional, Division of Emergency Medicine, Northwestern Community Hospital, Chicago, IL

2004 Associate, Division of Emergency Medicine, Northwestern Community Hospital, Chicago, IL

Oct 2004 - Present Staff Physician, The Hospital for Sick Children, Toronto, Ontario

May 1, 2005 - Nov 13, 2006 Project Director, Research Institute, The Hospital for Sick Children, Toronto, Ontario

Nov 13, 2006 - Present Associate Scientist, Child Health Evaluative Sciences Program, Research Institute, Hospital for Sick Children, Toronto, Ontario

Honours:


Division of Paediatric Emergency Medicine, Clinical Recognition Award-MD, Runner Up. In recognition of excellence in outstanding effort & contribution to the Emergency Department. 2006

Division of Paediatric Emergency Medicine, Research Recognition Award-MD. In recognition of excellence in outstanding effort & contribution to research. 2006

Publications:


Biographical Sketch

Name: Allan Coates
Title: Division of Respiratory Medicine
The Hospital for Sick Children
Professor of Pediatrics
University of Toronto

Education
Begin with baccalaureate or other initial professional education, and include all postdoctoral training.

<table>
<thead>
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<th>Institution and location</th>
<th>Degree</th>
<th>Year</th>
<th>Field of study</th>
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<tr>
<td>McGill University</td>
<td>B.Eng.(Elect.)</td>
<td>1967</td>
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<td>Montreal, Quebec</td>
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<tr>
<td>McGill University</td>
<td>M.D.C.M.</td>
<td>1972</td>
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</tr>
<tr>
<td>Montreal, Quebec</td>
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</table>

Previous Employment:
1977-1996 Full-time Member of the Respiratory Medicine Service, The Montreal Children’s Hospital
1984-1985 Acting Director, Newborn Medicine, The Montreal Children’s Hospital
1984-1996 Co-Director BPD Clinic, The Montreal Children’s Hospital
1987-1993 Director Cystic Fibrosis Clinic, The Montreal Children’s Hospital
1988-1989 Acting Director, Respiratory Medicine Service, The Montreal Children’s Hospital
1989-1996 Co-Director, McGill Respiratory Training Program
1989-1996 Director, Respiratory Medicine Service, The Montreal Children’s Hospital
1997-2005 Director, Division of Respiratory Medicine, Hospital for Sick Children
1998-2004 Associate Head in the Integrative Biology Program- Research Institute, Hospital for Sick Children
2005-2006 Staff Physician, Division of Respiratory Medicine, Hospital for Sick Children
2006-2015 Medical Director, Pulmonary Function Lab, Division of Respiratory Medicine, Hospital for Sick Children

Honours: N/A

Publications:


Principal Investigator: Suzanne Schuh

Biographical Sketch

Give the following information for key personnel, beginning with the principal investigator.

Name: Patricia Parkin

Title: Division of Pediatric Medicine
The Hospital for Sick Children
Associate Professor of Pediatrics
University of Toronto

Education

Begin with baccalaureate or other initial professional education, and include all postdoctoral training.

<table>
<thead>
<tr>
<th>Institution and location</th>
<th>Degree</th>
<th>Year</th>
<th>Field of study</th>
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</thead>
<tbody>
<tr>
<td>University of Toronto, Trinity College</td>
<td>B.Sc</td>
<td>1979</td>
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<tr>
<td>Toronto, ON</td>
<td></td>
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<tr>
<td>The Medical Council of Canada</td>
<td>LMCC</td>
<td>1982</td>
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<tr>
<td>Ottawa, Ontario</td>
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<tr>
<td>McMaster University Medical School</td>
<td>M.D</td>
<td>1982</td>
<td></td>
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<tr>
<td>Hamilton, Ontario</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>American Academy of Pediatrics Fellow</td>
<td>F.A.A.P.</td>
<td>1987</td>
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<tr>
<td>Royal College of Physicians and Surgeons of Canada</td>
<td>FRCP (C)</td>
<td>1987</td>
<td>Pediatrics</td>
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<tr>
<td>Ottawa, Ontario</td>
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Research or Professional Experience

Concluding with your present position, list in chronological order all previous employment, experience, and honors. List in chronological order complete references to all publications during the past three years and to representative earlier publications pertinent to this application.

Previous Employment:

1989 – Present
Active Staff Pediatrician, Division of Pediatric Medicine, The Hospital for Sick Children, Toronto, Ontario

1989 – 1997
Director, Pediatric Medicine Consult Team, Division of Pediatric Medicine, The Hospital for Sick Children, Toronto, Ontario

1990 – Present
Consultant Pediatrician, Pediatric Neurofibromatosis Clinic, Division of Pediatric Medicine, The Hospital for Sick Children, Toronto, Ontario

1994 – 1997
Director, Pediatric Medicine Inpatient Unit, Division of Pediatric Medicine, The Hospital for Sick Children, Toronto, Ontario

1997 – 2000
Acting Director, Pediatric Outcomes Research Team (PORT), Division of Pediatric Medicine, The Hospital for Sick Children, Toronto, Ontario

1997 – 2004
Head, Division of Pediatric Medicine, The Hospital for Sick Children, Toronto, Ontario

2004 – Present
Director, Pediatric Outcomes Research Team (PORT), The Hospital for Sick Children, Toronto, Ontario

2004 – Present
Director, Research and Fellowship Program, Division of Pediatric Medicine, The Hospital for Sick Children, Toronto, Ontario

Honours:

Harry Bain Award for Excellence in Clinical Teaching, Department of Pediatrics. University of Toronto, Hospital for Sick Children. 1999

Publications:


To insert another biographical sketch, make sure macros are enabled, and then press the ALT and 1 keys (ALT + 1). For instructions on enabling macros, see: http://office.microsoft.com/assistance/2002/articles/pwMacroSecurity.aspx
Biographical Sketch

Do not exceed two pages per biographical sketch.

Name: Upton Allen
Title: Director, Division of Infectious Diseases
The Hospital for Sick Children
Professor of Pediatrics
University of Toronto

Education

Begin with baccalaureate or other initial professional education, and include all postdoctoral training.

<table>
<thead>
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<th>Year</th>
<th>Field of study</th>
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</thead>
<tbody>
<tr>
<td>University of The West Indies, Kingston, Jamaica</td>
<td>MBBS</td>
<td>1981</td>
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<tr>
<td>McMaster University, Hamilton, Ontario</td>
<td>MSc</td>
<td>1990</td>
<td>Design Measurement and Evaluation</td>
</tr>
<tr>
<td>The Hospital for Sick Children, Toronto, Ontario</td>
<td>FRCPC, FAAP</td>
<td>1987</td>
<td></td>
</tr>
</tbody>
</table>

Research or Professional Experience

Concluding with your present position, list in chronological order all previous employment, experience, and honors. List in chronological order complete references to all publications during the past three years and to representative earlier publications pertinent to this application.

Previous Employment:

1991-1995: Assistant Professor of Pediatrics, Division of Infectious Diseases, Children’s Hospital of Eastern Ontario, University of Ottawa.

Program Director, Subspecialty Training in Pediatric Infectious Diseases, Children’s Hospital of Eastern Ontario, University of Ottawa.

Director, Pediatric HIV Clinic,
Children’s Hospital of Eastern Ontario

Consulting Staff (Infectious Diseases),
Ottawa General Hospital

11/2003-> current Chief, Division of Infectious Diseases, Hospital for Sick Children,
06/2005 -> current Senior Associate Scientist, Research Institute, Hospital for Sick Children.

2006 -> current Professor of Pediatrics, Division of Infectious Diseases, Department of Paediatrics
Hospital for Sick Children, University of Toronto

Honours:

2004 Appointed to Credentials Committee, Royal College of Physicians and Surgeons of Canada.
2005 Selected for Distinguished Poster Faculty session, Infectious Diseases Society of America Meeting, 2005.
2005 Promoted to Senior Associate Scientist, Research Institute, Hospital for Sick Children.
2005 Visiting Professor, Commission Training for Paediatrics, Hospital Authority, Hong Kong in Collaboration with the University of Hong Kong and the Chinese University of Hong Kong.
2006 Promoted to Full Professor, University of Toronto
2006 External Examiner, University of the West Indies, Jamaica
2006 Visiting Professor, University of Calgary

Publications:


Biographical Sketch

Do not exceed two pages per biographical sketch.

Give the following information for key personnel, beginning with the principal investigator.

Name: Andrew Willan
Title: Senior Scientist, Population Health Sciences
The Hospital for Sick Children
Professor of Department of Public Health Sciences
University of Toronto

Education
Begin with baccalaureate or other initial professional education, and include all postdoctoral training.

<table>
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<th>Degree</th>
<th>Year</th>
<th>Field of study</th>
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</thead>
<tbody>
<tr>
<td>Department of Epidemiology and Biostatistics University of Western Ontario, London ON</td>
<td>PhD</td>
<td>1979</td>
<td>Biostatistics</td>
</tr>
<tr>
<td>Queen's University, Kingston ON</td>
<td>MSc</td>
<td>1976</td>
<td>Statistics</td>
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<tr>
<td>Queen's University, Kingston ON</td>
<td>Bed</td>
<td>1972</td>
<td>Mathematics and Physical Education</td>
</tr>
<tr>
<td>York University, Toronto ON</td>
<td>BA</td>
<td>1970</td>
<td>Economics and Mathematics</td>
</tr>
</tbody>
</table>

Research or Professional Experience

Concluding with your present position, list in chronological order all previous employment, experience, and honors. List in chronological order complete references to all publications during the past three years and to representative earlier publications pertinent to this application.

Previous Employment:
September 1981 to August 1987 - Assistant Professor, Department of Community Health and Epidemiology, Queen's University, Kingston ON.

April 1985 to August 1987 - Head of Biometry with the Clinical Trials Group, National Cancer Institute of Canada, Queen's University, Kingston ON.

September 1987 to February 1989 - Associate Professor, Department of Population Medicine, University of Guelph, Guelph ON

March 1989 to October 1991 - Associate Professor, Department of Preventive Medicine and Biostatistics, University of Toronto, Toronto ON

January 1989 to May 1990 - Head, Division of Clinical Trials and Epidemiology, Sunnybrook Health Science Centre, Toronto ON

September 1990 to June 1993 - Associate Professor, Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton ON

September 1993 to June 2002 - Professor, Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton ON

Senior Scientist, Population Health Sciences, SickKids Research Institute, Toronto
Professor, Population Health Sciences, University of Toronto
Professor Emeritus, Clinic Epidemiology and Biostatistics, McMaster University

Honours:
Co-author on a paper receiving the International Society for Pharmaco-economics and Outcomes Research Award for Methodology Excellence, awarded May 2003.
Co-author on a paper receiving the International Society for Pharmacoeconomics and Outcomes Research Award for Methodology Excellence, awarded May 2002.

**Publications:**


16. Eckermann S, **Willan AR**. Expected value of information and decision making in HTA. *Health Economics* 2007; **16**: 195-209. CPA


Biographical Sketch

Do not exceed two pages per biographical sketch.

Give the following information for key personnel, beginning with the principal investigator.

Name: Wendy Ungar

Title: Senior Scientist, Population Health Sciences
Associate Professor, Department of Health Policy, Management and Evaluation, Faculty of Medicine, University of Toronto
Adjunct Scientist, Institute for Clinical Evaluative Sciences

Education Begin with baccalaureate or other initial professional education, and include all postdoctoral training.

<table>
<thead>
<tr>
<th>Institution and location</th>
<th>Degree</th>
<th>Year</th>
<th>Field of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>University of Toronto, Ontario, Canada</td>
<td>Ph.D.</td>
<td>1997</td>
<td>Faculty of Medicine</td>
</tr>
<tr>
<td>McGill University, Montreal, Quebec, Canada</td>
<td>M.Sc.</td>
<td>1984</td>
<td>Pharmacology and Therapeutics</td>
</tr>
<tr>
<td>Brandeis University, Boston, Massachusetts, U.S.A.</td>
<td>B.A</td>
<td>1981</td>
<td>Biology</td>
</tr>
</tbody>
</table>

Research or Professional Experience

Concluding with your present position, list in chronological order all previous employment, experience, and honors. List in chronological order complete references to all publications during the past three years and to representative earlier publications pertinent to this application.

Previous Employment:

1985-1987 Research Associate, Pharmaceutical Clinical Research, Bristol-Myers Pharmaceutical Group, Ottawa, Ontario
1987-1990 Manager, Pharmaceutical Clinical Research, Bristol-Myers Pharmaceutical Group, Ottawa, Ontario
1991-1993 Associate Director/Clinical Project Manager, Ciba-Geigy Canada Ltd., Mississauga, Ontario
1996-1997 Health Economics and Health Services Research Consultant
1999-2005 Associate Member, Faculty of Graduate Studies, University of Toronto
1999-2006 Assistant Professor, Department of Health Policy, Management and Evaluation, University of Toronto
1999-2006 Scientist, Population Health Sciences, Hospital for Sick Children
2005-present University of Toronto Program Director, International Masters Degree in Health Technology Assessment & Management (Ulysses Program)
2006-present Associate Professor, Department of Health Policy, Management and Evaluation, University of Toronto

Honours:

2002-2007 New Investigator Award, Canadian Institutes of Health Research
2005 Canadian Health Services Research Foundation CAN! Award
2006 Canadian Health Services Research Foundation CAN! Award

Publications:


To insert another biographical sketch, make sure macros are enabled, and then press the ALT and 1 keys (ALT + 1). For instructions on enabling macros, see: http://office.microsoft.com/assistance/2002/articles/swMacroSecurity.aspx
Biographical Sketch

Do not exceed two pages per biographical sketch.

Give the following information for key personnel, beginning with the principal investigator.

Name: Zelia Da Silva
Title: Registered Respiratory Therapist
Department of Respiratory Therapy
The Hospital for Sick Children

Education

Begin with baccalaureate or other initial professional education, and include all postdoctoral training.

<table>
<thead>
<tr>
<th>Institution and location</th>
<th>Degree</th>
<th>Year</th>
<th>Field of study</th>
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<tbody>
<tr>
<td>The Michener Institute for Applied Health Sciences, Toronto, Ontario</td>
<td>Respiratory Therapy Program</td>
<td>1993</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clinical Teaching Techniques Certificate Course</td>
<td>1997</td>
<td></td>
</tr>
<tr>
<td>Critical Care Unit</td>
<td>ECMO Specialist - Didactic and Clinical Training</td>
<td>1998</td>
<td></td>
</tr>
<tr>
<td>The Hospital for Sick Children</td>
<td>Master of Applied Science (Respiratory Science)</td>
<td>Collaborative</td>
<td>2004-</td>
</tr>
<tr>
<td></td>
<td>Michener/Charles Sturt University Degree Completion Program</td>
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</table>

Research or Professional Experience

Concluding with your present position, list in chronological order all previous employment, experience, and honors. List in chronological order complete references to all publications during the past three years and to representative earlier publications pertinent to this application.

Previous Employment:

- August 1993 – February 1997  Staff Therapist, CCU, NICU, Acute Care (Wards/ER)
  The Hospital For Sick Children
- July 2003 – July 2004   Acting Clinician Educator, Respiratory Therapy- MLOA
  The Hospital For Sick Children
- February 1997 – April 2005  Clinical Coordinator, Respiratory Therapy / Michener Institute
  The Hospital For Sick Children
- April 2005 – Present  Profession Leader, Respiratory Therapy
  The Hospital For Sick Children

Honours:
The Michener Institute for Applied Health Sciences
Recipient of the 1993 Student Achievement Award

Publications:
“Efficacy of Optimal Versus Traditional Delivery of Humidity in Children with Croup”
**Reviewer Information**

Please provide the names of four persons who have the expertise and competency to review your proposed project. State your present or past relationship with them, if any. When recommending reviewers, **avoid any basis for potential conflict of interest** or concern regarding peer reviewer objectivity.

<table>
<thead>
<tr>
<th>1. Name</th>
<th>Degree</th>
<th>Title</th>
<th>Address</th>
<th>City</th>
<th>State</th>
<th>Zip code</th>
<th>Telephone</th>
<th>Fax</th>
<th>Email</th>
<th>Relationship to investigator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr. David Johnson</td>
<td>MD</td>
<td>Associate Professor of Pediatrics, University of Calgary, Alberta Children’s Hospital</td>
<td>1820 Richmond Road S.W.</td>
<td>Calgary</td>
<td>AB</td>
<td>T2T 5C7</td>
<td>403-943-7507</td>
<td>403-943-7649</td>
<td><a href="mailto:David.Johnson@calgaryhealthregion.ca">David.Johnson@calgaryhealthregion.ca</a></td>
<td>None</td>
</tr>
<tr>
<td>Dr. Joseph Zorc</td>
<td>MD</td>
<td>Emergency Physician and Investigator, The Children’s Hospital of Philadelphia</td>
<td>34th and Civic Center Blvd.</td>
<td>Philadelphia</td>
<td>PA</td>
<td>19104</td>
<td>215-590-1944</td>
<td>215-590-4454</td>
<td><a href="mailto:zorc@email.chop.edu">zorc@email.chop.edu</a></td>
<td>None</td>
</tr>
<tr>
<td>Dr. Dele Davies</td>
<td>MD</td>
<td>Professor of Pediatrics, Michigan State University</td>
<td>B240 Life Science</td>
<td>East Lansing</td>
<td>MI</td>
<td>48824-1317</td>
<td>517-355-3308</td>
<td>Fax</td>
<td><a href="mailto:daviesdc@msu.edu">daviesdc@msu.edu</a></td>
<td>None</td>
</tr>
<tr>
<td>Dr. Michael Schull</td>
<td>MD</td>
<td>Emergency Physician and Research Scientist, ICES</td>
<td>G1 06-2075 Bayview Avenue</td>
<td>Toronto</td>
<td>ON</td>
<td>M4N 3M5</td>
<td>416-480-4055 ext. 3793</td>
<td>Fax</td>
<td><a href="mailto:mjss@ices.on.ca">mjss@ices.on.ca</a></td>
<td>None</td>
</tr>
</tbody>
</table>

**Principal Investigator:** Suzanne Schuh  
**Project Name:** Impact of Oximetry on Disposition in Acute Bronchiolitis
# Project Application—Thrasher Research Fund

## Title
Provide a descriptive title rather than a general title

Impact of Oximetry on Disposition in Acute Bronchiolitis

## Principal Investigator
Specify one person who is responsible to the Thrasher Research Fund for the scientific and/or technical work of the project. This individual is responsible for grant-related correspondence and expenditures.

| Name and address | Suzanne Schuh  
c/o The Hospital for Sick Children  
Department of Emergency Medicine  
555 University Ave.  
Toronto, ON  
Canada |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Telephone</strong></td>
<td>416-813-6239</td>
</tr>
<tr>
<td><strong>Fax</strong></td>
<td>416-813-5043</td>
</tr>
<tr>
<td><strong>E-mail</strong></td>
<td><a href="mailto:Suzanne.Schuh@sickkids.ca">Suzanne.Schuh@sickkids.ca</a></td>
</tr>
</tbody>
</table>

## Co-principal Investigator(s)
List additional individuals who are responsible for the scientific and/or technical work of the project.

| Name(s) and institution(s) | Stephen Freedman – The Hospital for Sick Children  
Allan Coates - The Hospital for Sick Children  
Patricia Parkin - The Hospital for Sick Children  
Upton Allen - The Hospital for Sick Children  
Andrew Willan - Research Institute, The Hospital for Sick Children  
Wendy Ungar – Research Institute, The Hospital for Sick Children  
Zelia Da Silva - The Hospital for Sick Children |
|-----------------------------|--------------------------------------------------|

## Human Subjects?
If yes, complete the enclosed Protection of Human Subjects form.

<table>
<thead>
<tr>
<th>Form Status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>X</strong> Yes</td>
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<tr>
<td><strong>No</strong></td>
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<tr>
<td><strong>Included</strong></td>
</tr>
<tr>
<td><strong>NA</strong></td>
</tr>
</tbody>
</table>

## Animals Used?
If yes, document compliance with Animal Welfare Assurance laws.

<table>
<thead>
<tr>
<th>Form Status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Yes</strong></td>
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<tr>
<td><strong>X</strong> No</td>
</tr>
<tr>
<td><strong>Included</strong></td>
</tr>
<tr>
<td><strong>NA</strong></td>
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</tbody>
</table>

## Project Period
The entire project may not exceed 3 years. The project start date will be determined in consultation with Thrasher Research Fund staff.

<table>
<thead>
<tr>
<th>Approximate start date (month and year)</th>
<th>December 1, 2007</th>
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<tbody>
<tr>
<td>Approximate end date (month and year)</td>
<td>April 30, 2010</td>
</tr>
</tbody>
</table>

## Total Budget Request
$ 285,136

## Performance Site(s)
Indicate where the work described in the “Experimental Design and Methodology” section will be performed. Please provide specific organization names and their complete addresses, including zip/postal code, telephone number, fax number, and email.

<table>
<thead>
<tr>
<th>Organization name and address</th>
<th>Organization name and address</th>
</tr>
</thead>
</table>
| The Hospital for Sick Children  
Pediatric Emergency Department  
555 University Ave.  
Toronto, ON  
Canada  
Tel: 416-813-5807  
Fax: 416-813-5043 |

## Supervising Institution
Name the one organization that will be legally and financially responsible and accountable for the use and disposition of any funds awarded on the basis of this application.

| Supervising institution name and address | Phone (416) 813-5723  
Fax (416) 813-5085  
Email AnneMarie.Christian@sickkids.ca |
|----------------------------------------|------------------|
| The Hospital for Sick Children  
555 University Ave.  
Toronto, ON  
Canada |

## Official Signatures for Supervising Institution
We, the undersigned, certify that the statements herein are true and complete to the best of our knowledge and that facilities are available for the proposed research. We will comply with the Thrasher Research Fund’s Conditions of Grant and requirements for reporting that are in effect at the time of the award.

<table>
<thead>
<tr>
<th>Name and title of principal investigator</th>
<th>Signature</th>
<th>Date (mm/dd/yy)</th>
</tr>
</thead>
</table>
| Suzanne Schuh  
Staff Emergency Physician and Research Director  
Division of Pediatric Emergency Medicine  
Senior Associate Scientist, Research Institute  
Professor of Pediatrics, University of Toronto |
| **Signature** | **Date** |

<table>
<thead>
<tr>
<th>Name and title of principal investigator</th>
<th>Signature</th>
<th>Date (mm/dd/yy)</th>
</tr>
</thead>
</table>
| Suzanne Schuh  
Staff Emergency Physician and Research Director  
Division of Pediatric Emergency Medicine  
Senior Associate Scientist, Research Institute  
Professor of Pediatrics, University of Toronto |
<p>| <strong>Signature</strong> | <strong>Date</strong> |</p>
<table>
<thead>
<tr>
<th>Name and title of department chairman, if applicable</th>
<th>Signature</th>
<th>Date (mm/dd/yy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norm Rosenblum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pediatrician-in-Chief</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The Hospital for Sick Children</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chairman, Department of Pediatrics</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Name and title of official from supervising institution</td>
<td>Signature</td>
<td>Date (mm/dd/yy)</td>
</tr>
<tr>
<td>Ms. Anne Marie Christian</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vice President, Research Operations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Associate Chief, Research Institute</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The Hospital for Sick Children</td>
<td></td>
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</tr>
</tbody>
</table>
# Protection of Human Subjects Assurance/Certification/Declaration

Thrasher Research Fund

**Policy** A research project involving human subjects sponsored by a U.S.-based institution that is not exempt from HHS regulations may not be funded unless an institutional review board (IRB) has reviewed and approved the activity in accordance with Section 474 of the Public Health Service Act as implemented by Title 45, Part 46, of the Code of Federal Regulations (45 CFR 46-as revised). The applicant institution must submit certification of IRB approval to the Thrasher Research Fund unless the applicant institution has designated a specific exemption under Section 46.101(b) that applies to the proposed research project. Institutions with an assurance of compliance on file with HHS that covers the proposed project should submit certification of IRB review and approval with each application. In the case of institutions that do not have an assurance of compliance on file with HHS covering the proposed project, certification of IRB review and approval must be submitted within 30 days of the receipt of a written request from HHS for certification. Documentation of IRB approval from all project-related participating institutions must be included.

**Title of application** Impact of Oximetry on Disposition in Acute Bronchiolitis

**Principal investigator** Suzanne Schuh

**Investigational New Drug Exemption** If more than one is involved, list others under notes below.

**Food and Drug Administration required information** In accordance with 45 CFR 46.121, if an application is made to HHS requiring certification and involving use of an investigational new drug or device, additional information is required. Thirty (30) days must elapse between date of receipt by FDA of Form FD-1571 and use of the drug, unless the 30-day delay period is waived by FDA (21 CFR 312.1).

**Sponsor name**

**Drug name**

**Date of end of 30-day expiration or waiver**

**Number issued**

**HHS Assurance Status**

- [ ] This institution has an approved assurance of compliance on file with HHS which covers this activity.
- [ ] No assurance of compliance which applies to this activity has been established with HHS, but upon request the applicant institution will provide written assurance of compliance and certification of IRB review and approval in accordance with 45 CFR 46.

**Certification of IRB Review or Declaration of Exemption**

- [ ] This activity has been reviewed and approved by an IRB in accordance with the requirements of 45 CFR 46, including its relevant subparts. This certification fulfills, when applicable, requirements for certifying FDA status for new investigational drug or device.

**Date of IRB approval**

**Follow-up certification is required.**

**Full Board Review**

**Expedited Review**

- [ ] This activity contains multiple projects, some of which have not been reviewed. The IRB has granted approval on condition that all projects covered by 45 CFR 46 will be reviewed and approved before they are initiated and that appropriate further certification (Form HHS 5156) will be submitted.
- [ ] Human subjects are involved, but this activity qualifies for exemption under 46.101(b) in accordance with paragraph [insert paragraph number of exemption in 46.101(b), 1 through 5], but the institution did not designate that exemption on the application.

Each official signing below certifies that the information provided on this form is correct and that each institution assumes responsibility for assuring required future reviews, approvals, and submissions of certification.

**Application institution**

**Cooperating institution**

<table>
<thead>
<tr>
<th>Name, address, telephone and e-mail</th>
<th>Name, address, telephone and e-mail</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr. Melvin Freedman 555 University Ave. Toronto, ON Tel: 416-813-6152 e-mail: <a href="mailto:melvin.freedman@sickkids.ca">melvin.freedman@sickkids.ca</a></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Name and title of official</th>
<th>Name and title of official</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr. Melvin Freedman, MD, CRCP(C), FRCP(C), FAAP Senior staff physician Chair, Research Ethics Board</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Signature of official</th>
<th>Date</th>
<th>Signature of official</th>
<th>Date</th>
</tr>
</thead>
</table>
Impact of Oximetry on Disposition in Acute Bronchiolitis

Lay Abstract

The Lay Abstract should read in such a way that a person not familiar with the proposed research could understand the objectives and intended practical outcomes of the project. The abstract serves as a succinct and accurate description of the proposed work when separated from the application. This information is directed specifically to the Executive Committee members as they make final funding decisions.

Background—Bronchiolitis is the most common lower respiratory tract infection in infants, characterized by wheezing and breathing distress. It is responsible for 90,000 hospitalizations annually, at a cost of $700 million US.

Since 1980, the proportion of children hospitalized with bronchiolitis has risen by 2.5 fold while mortality has remained unchanged. Since 20 years ago infants with bronchiolitis have been routinely undergoing continuous or frequent monitoring of the amount of oxygen in their blood through special skin probes (oxygen saturation). Oxygen saturation is then used to decide on supplemental oxygen therapy. Although textbooks define a significantly low oxygenation as a saturation under 90%, the threshold for giving supplemental oxygen varies widely, is frequently higher and depends on individual and local practices since previous studies have not addressed this issue. Indeed, over the years saturation has even become one of the main criteria for hospitalization, often irrespective of the amount of breathing distress the child is in. Numerous infants with only mild discomfort and a mild decrease in saturation who previously would have been discharged home are now being admitted.

Preliminary evidence suggests that this change in practice may be at least in part responsible for this dramatic increase in admissions, and several authors question the benefits of relying mainly on oxygen saturation for hospitalization. Recent American Academy of Pediatrics (AAP) bronchiolitis guidelines suggest that infants with oxygen saturation of 90% and above are unlikely to benefit from supplemental oxygen and call for studies on the most efficient use of oxygen and of oximetry monitoring. However, this recommendation is based on physiologic principles and has not been tested in practice. This is the first study seeking to examine if the hospitalization decision in bronchiolitis should be determined primarily by clinical assessment and if infants who are otherwise well enough to go home whose saturation is above or in the vicinity of that recommended by the AAP for supplemental oxygen therapy can be safely discharged.

The primary objective in previously healthy infants diagnosed with acute bronchiolitis in a pediatric emergency department (ED) to compare the rate of hospitalization within 72 hours in those whose oxygen saturation measurements are set consistently 3% above the true values versus those in whom saturation measurements represent true values.

To date, only two studies of oxygen saturation in bronchiolitis have been done; one consisted of a survey using imaginary clinical scenarios and the other was a retrospective inpatient study. The former study showed that a physiologically unimportant difference in saturation of 2% would potentially result in a two-fold difference in hospitalization. Our study should answer whether this indeed happens in real life and whether the discharge decision should be decided primarily clinically. The latter paper demonstrated that hospitalized infants with bronchiolitis who meet clinical discharge criteria stay in hospital on average an extra 1.6 days due to persistent mild decrease in oxygen saturation.

Design—Previously healthy infants 6 weeks to 12 months of age with bronchiolitis and with saturation ≥ 90% will be eligible. Children with severe bronchiolitis, other significant illnesses or prematurity will be excluded. They will be randomized to undergo management with intermittent oximetry using either true oxygen saturation measurements or saturation measurements set three percentage points above true values. Neither physicians, parents or study nurses will be aware of the group assignment, i.e. they will not know if the saturation measurement displayed corresponds to the true value. Primary outcome will be the rate of hospitalization within 72 hours in the two groups. Secondary outcomes will include the rate of supplemental oxygen therapy, unscheduled visits for bronchiolitis within 72 hours, length of ED stay and economic analysis.

Potential Impact—This study will have immediate impact on management. Based on the results we should find out if clinical assessment should play a primary role in the decision regarding disposition and if children who are otherwise well enough to go home and have saturations above or close to the threshold recommended by the AAP can be successfully discharged. It will also hopefully shed some light on the probability of therapeutic failure (i.e. admission within 72 hours) in children whose oxygenation is within a relatively narrow range of the safety limits recommended by the AAP, thereby eliminating the bias to admit created by the presence of mild and clinically insignificant decrease in oxygenation. If the current practice of oximetry with the highly variable and higher thresholds for oxygen therapy indeed significantly contributes to the alarming rise in hospitalizations in bronchiolitis, proper use and interpretation of this technology may lead to fewer hospitalizations and thereby reduce the burden on the children and their caretakers.
Scientific Abstract (Do not exceed one page.)

Summarize the proposal's objectives and specific aims, making reference to how the project relates to health, and describe concisely the methodology for achieving these goals. The abstract serves as a succinct and accurate description of the proposed work when separated from the application. This information is directed specifically to the Advisory Committee and peer reviewers who are conversant with the area of the proposed research.

Objectives/ Specific Aims – Bronchiolitis is the most common lower respiratory tract infection in infants, responsible for 90,000 hospitalizations annually, at a cost of $700 million US. Since 1980, the proportion of children hospitalized for bronchiolitis has risen by 250% while mortality has remained unchanged. Since 20 years ago infants with bronchiolitis have been routinely undergoing oxygen saturation monitoring, the results of which are then used to decide on supplemental oxygen therapy. The threshold for giving supplemental oxygen varies widely from 90 to 94% and depends on local practices due to lack of evidence-based guidelines. Over the years saturation has even become one of the main criteria for hospitalization, often irrespective of the degree of respiratory distress. Numerous infants with minimal distress and mild hypoxia who previously would have been discharged are now being admitted. Preliminary evidence suggests that this change in practice may be at least in part responsible for this dramatic increase in admissions, with physicians assigning greater significance to oximetry than to the physical examination. However, it is limited by retrospective design and by the use of hypothetical vignettes. Specifically, postulated saturation of 92% resulted in 83% planned admission rate, which was double the hospitalization rate for saturation of 94%, irrespective of the degree of respiratory distress. Experts question the merits of the frequent use of oximetry and of relying primarily on saturation as a criterion for disposition. Recent American Academy of Pediatrics (AAP) bronchiolitis guidelines suggest that previously healthy infants with oxygen saturation of 90% and above are unlikely to benefit from supplemental oxygen and call for studies on the most efficient use of oxygen and of oximetry monitoring. We hypothesize that the hospitalization rate of children who according to the ED physicians meet clinical criteria for discharge and whose saturation display has been falsely increased by three percentage points above the true values will be significantly lower than that of their counterparts whose physicians are presented with the true measurements. We plan the following specific aims:

1. In previously healthy children with bronchiolitis, to compare the rate of hospitalization within 72 hours of arrival at the index ED visit in patients whose oxygen saturation display is manipulated three percentage points above the true measurements versus those in whom the measurements correspond to the true values.

2. To compare the rate of supplemental oxygen therapy and length of stay as well as of unscheduled medical visits for bronchiolitis within 72 hours in the two groups.

3. To determine if there is a significant association between the difference in the primary outcome between the groups and the patients' age and disease severity.

4. To determine the incremental costs/savings gained from the societal perspective in the two study groups.

Methodology

Study design: Randomized double blind single center trial.

Study population: Previously healthy children 6 weeks to 12 months of age with the first episode of acute bronchiolitis, with baseline Respiratory Disease Assessment Instrument (RDAI) ≥3 and true oxygen saturation ≥90%.

Exclusion criteria: Pre-existing pulmonary or cardiac disease, neuromuscular disease or chronic hypoxia, severe respiratory distress (retraction component of RDAI ≥8 out of 9 points), room air oxygen saturation <90%, history of prematurity or unavailability of telephone.

Study procedure: Screening for eligibility and consent will take place in the ED triage. True oxygen saturation of eligible infants will be taken by the study coordinator and will only be entered in the patient chart in the event of non participation or after conclusion of the intervention. After enrolment, the patients will be randomized by an internet randomization service to those undergoing hourly saturation monitoring using either true oxygen saturation measurements or measurements which have been set 3% above the true values, the research nurse, ED staff and parents will thus be blinded to true saturations. The ED physicians will be encouraged to use supplemental oxygen based on their clinical assessment (irrespective of the saturation) and their interpretation of the displayed saturation measurement. All children will receive one standardized dose of nebulized albuterol 2.5mg/ dose. Primary outcome will be hospitalization within 72 hours, defined as admission to our inpatient ward, transfer to another inpatient facility or the need for bronchiolitis therapy at the index visit lasting more than six hours. Secondary outcomes will be supplemental oxygen therapy, length of stay in the ED and unscheduled return for care within 72 hours; an economic assessment will also be done. The research coordinator will assess the oxygen saturation, respiratory rate, RDAI score and the disposition plan at baseline and hourly thereafter up to 360 minutes or disposition, whichever comes first. He/she will also measure the secondary outcomes and collect the data needed to estimate costs/savings in the two groups. Unscheduled return for care and delayed hospitalizations following initial discharge will be determined during telephone follow-ups at 72 hours.
Hypothesis(es) to be Tested

Preliminary evidence and expert opinion suggest over-reliance on oximetry in the disposition decision in bronchiolitis and the likely contribution of this practice to the recent dramatic rise in hospitalizations in this disease. If this is so, blinding the ED physicians to oxygen saturations and by falsely raising the displayed values by an amount which is physiologically insignificant but widely perceived to be clinically relevant should result in hospitalization rates which are significantly lower than in those whose physicians are presented with true saturations. In this randomized double blind trial we hypothesize that previously healthy infants with bronchiolitis whose emergency department physicians are blinded to true oximetry measurements and in whom the oximetry measurements are elevated three percentage points above true values will have hospitalization rates within 72 hours of presentation at the index visit at least 15% lower compared to those whose physicians see true saturations. The impact of this intervention will also be assessed by comparing the proportions of infants receiving supplemental oxygen, unscheduled medical visits within 72 hours of presentation, length of stay and the incremental costs/savings in the two groups.

Specific Aim(s) of the Project

1. In previously healthy children with bronchiolitis undergoing hourly oximetry measurements, to compare the rate of hospitalization within 72 hours of presentation in those whose emergency physicians are presented with true oxygen saturation measurements versus those whose oxygen saturation measurement display is raised 3% above respective true values.

Hospital admission constitutes an important outcome since it carries a major impact on the family and the health care system. However, for clinicians to accept that children with bronchiolitis who have saturation in the vicinity of 90% or higher and who otherwise meet discharge criteria can be sent home, not only must it be shown to be effective but it must also be safe. Although previous studies have not found that a mild reduction in oxygenation is linked to progression of disease severity, they have not employed specific protocols focusing on this critical issue. We shall assess this by comparing the proportions of hospitalizations either at the index ED visit or within the next 72 hours since this later group clearly will not have been successfully discharged. Hospital admission within 72 hours thus incorporates the outcome of both the immediate disposition and safety. This will be the first randomized double-blind controlled trial examining clinical impact of blinding the emergency physicians to true oxygen saturations by presenting them with either true or falsely elevated measurement values. Since the infants in the altered saturation group will have real saturations comparable to those in the true saturation group, finding a significant difference will likely be due to the differential interpretation of displayed measurements in mildly hypoxic children. The study will help us determine if children with bronchiolitis who have saturations around 90% or higher can be successfully discharged. The study will also shed light on the frequently asked question if well looking infants with saturations in the very high 80s/low 90s are at a high risk of subsequent admission to hospital.

2. To compare the rate of supplemental oxygen therapy and length of stay in the two groups as well as the rate of unscheduled medical visits for bronchiolitis within 72 hours. If our primary hypothesis proves correct, we may also find that significantly fewer patients in the altered saturation group will receive supplemental oxygen since many infants with mild hypoxia have only a mildly increased work of breathing which by itself would not prompt this intervention. Likewise, these patients may be discharged sooner since the physicians may not feel as obligated to observe them further “just in case”. In this scenario, we anticipate the rate of unscheduled visits would be comparable in both groups. We do not consider unscheduled medical visits to reflect safety, since many of these visits will require reassurance/education only and will not result in major management changes such as hospitalization.

3. To determine if there is a significant association between the difference in the primary outcome between the groups and the patients’ age and disease severity.

4. To determine the incremental costs/savings gained from the societal perspective in the two study groups. Economic evaluations indicate that the major societal cost associated with RSV related lower respiratory tract infections is hospitalization. If our hypothesis proves correct we would anticipate significant savings associated with determining hospitalization mainly clinically compared to the disposition dictated by variable saturation thresholds.
Bronchiolitis is a viral syndrome characterized by rhinorrhea, wheezing and respiratory distress, accounting for 16% of all hospitalizations in the first year of life, at a cost of $700 million US dollars. Its management is complicated by uncertainty due to lack of evidence over the optimal treatments and correlates more with local hospital or individual preferences than with disease severity. Therefore, there is a propensity to persist in practices of questionable benefit. Furthermore, the intensity of management is the main determinant of resource utilization and costs. Since the benefit of pharmacotherapy in bronchiolitis is controversial, supportive care such as oxygen therapy plays a major role. Infants with bronchiolitis undergo routine oximetry in the Emergency Department (ED), and oxygen is administered to those determined to be hypoxicemic. The aforementioned variation and lack of best practice consensus is relevant to when to initiate supplemental oxygen and whether or not clinical assessment should constitute the primary deciding factor with respect to disposition.

Pulse oximetry has been used since the mid 1980s and may have led to new criteria for hospitalization. Since its use became routine, the rate of hospitalization for bronchiolitis has increased by nearly 250% but mortality has remained unchanged. Concurrently, pediatric hospitalization rates for other lower respiratory tract diseases have not changed and those for other diseases have been decreasing. Although increased day care attendance may also contribute to this dramatic rise in bronchiolitis hospitalizations, several experts hypothesize that the use of frequent/continuous oximetry as well as its inconsistent interpretation with respect to when to initiate oxygen therapy may be largely responsible for this trend.

There is little evidence as to when supplemental oxygen is required, with guidelines ranging from 90%-94%. Without evidence delineating the associated risks and benefits, As a result, many infants with mild distress with saturations mildly diminished in the vicinity of 90% are admitted for oxygen therapy, regardless of the degree of respiratory distress, duration of desaturation, or state of wakefulness. Mild hypoxemia in bronchiolitis need not be accompanied by significantly increased work of breathing. For example, brief desaturations frequently occur after bronchodilator therapy and during sleep, without any change in the respiratory status. Oxygen saturation seems to have emerged as an overriding criterion for hospitalization from the Emergency Department (ED) and for discharge from the inpatient ward. An editorial commented that we have “…come to worship at the shrine of numbers…and that when the information is expressed in digits the truth is revealed.” Prior to the adoption of oximetry, many of these admitted infants would have been discharged. Evidence suggests that previously healthy children hospitalized with bronchiolitis are unlikely to deteriorate. Among outpatients, there is no consistent evidence that a mild reduction in oxygenation predicts progression of bronchiolitis.

Only two studies have addressed the impact of oxygen saturation in bronchiolitis: one is a retrospective review and the other consists of hypothetical vignettes. The former inpatient study demonstrated that the perceived need for supplemental oxygen based on oximetry when other discharge criteria are met prolongs hospital stay in 26% of infants by an average of 1.6 days at a cost of $1500 US per hospitalization. The accompanying editorial concludes that prospective studies of the utility of oximetry should be carried out, along with a critical analysis of costs and benefits. The second study surveyed the American Academy of Pediatrics (AAP) members on their treatment preferences in bronchiolitis and found that a minimal and physiologically insignificant difference in oxygen saturation between 92% and 94% with identical respiratory rates produces a two-fold increase in intended hospitalization rates. This study illustrates that small differences in oxygen saturation have major impact on disposition.

The current devotion to oximetry and its variable interpretation have therefore created a potential for misuse. Specifically, infants with mild hypoxemia and those with brief dips in saturation during sleep who otherwise meet clinical criteria for discharge are often admitted. Hospitalizations are expensive and not without risks. Recent AAP guidelines on bronchiolitis management suggest that previously healthy children with saturations 90% or higher are unlikely to benefit from supplemental oxygen and recommend research on the most efficient use of oxygen and oxygen monitoring in this disease. However, this recommendation consists of an expert consensus based on physiological principles and has not been prospectively validated.

This is the first bronchiolitis study to examine the clinical and economic impact of making disposition decision on primarily clinical grounds, while blinding the physicians to oxygen saturations by providing them with either true saturation measurements or those which are 3 percentage points above the true values. Although physiologically insignificant and within the measurement error of the instrument, this difference has been shown to be perceived as clinically relevant and to have a major hypothetical impact on disposition, without any evidence to support this belief. We hope to find out if children with oxygen saturations above or in the vicinity of the threshold recommended for initiation of oxygen therapy by the AAP can be safely discharged based on their clinical appearance rather than to have their hospitalization dictated by a locally defined number. This study will hopefully provide much needed evidence necessary to help us interpret the oximetry results more meaningfully which may in turn lead to fewer hospitalizations, shorter length of hospital stay and lower health care costs.
Principal Investigator: Suzanne Schuh

Supportive Preliminary Data

Include research conducted by the investigator(s) that leads to the present proposed research project. Do not exceed one page. Include literature references in the Literature References page provided.

Dr. Suzanne Schuh is a staff emergency pediatrician and a clinician investigator at the Hospital for Sick Children, with a cross-appointment as a Senior Associate Scientist in the Population Health Sciences program at the Hospital for Sick Children Research Institute. Her focus is the investigation of optimizing management of children with acute asthma, bronchiolitis and croup. Her previous studies involving numerous randomized controlled trials on these illnesses have addressed the efficacy of various aspects of pharmacotherapy such as inhaled bronchodilators and systemic corticosteroids. A paper recently published by the Journal of Pediatrics investigated the utility of chest radiographs in bronchiolitis and found that this investigation is usually not indicated since it rarely yields new useful information. The results of this paper were also introduced as a platform presentation at the annual Pediatric Academic Society meeting in San Francisco in April 2006. The proposed study constitutes a logical subsequent step in the investigation of this common disease.

A previous study by the PI of this proposal also examined the predictive value of oxygen saturation in hospitalization in acute asthma. Prior to its publication, the peer reviewers have brought up the issue of the likely bias in disposition created by the knowledge of the saturation and individual practice variation. This study should minimize this problem.

Dr. Stephen Freedman is a staff emergency paediatrician at the Hospital for Sick Children and an Associate Scientist in the Population Health Sciences program at the Hospital for Sick Children Research Institute. His research interest is optimizing management and resource utilization in children in the acute care setting, with a publication record in high impact journals such as the New England Journal of Medicine.

Dr. Allan Coates is a senior staff respirologist at the Hospital for Sick Children and a Senior Scientist at the Hospital for Sick Children Research Institute. He has both clinical expertise and an extensive publication record with respect to various aspects of management of children with acute respiratory compromise.

Dr. Patricia Parkin is a staff physician in the Division of Pediatric Medicine at the Hospital for Sick Children and an Associate Scientist in the Population Health Sciences program at the Hospital for Sick Children Research Institute. Her research concentrates on the diagnosis, prevention and treatment of common pediatric problems including acute asthma. She had also collaborated with Dr. Schuh on several trials including the aforementioned study focusing on oxygen saturation in disposition of children with acute asthma.

Dr. Upton Allen is a staff physician in the Infectious Disease Division at the Hospital for Sick Children and a Senior Associate Scientist in the Population Health Sciences program at the Hospital for Sick Children Research Institute. He has an extensive track record as a widely published senior investigator in this field, with numerous CIHR funded trials. He has also collaborated with Dr. Schuh on several previous studies, including the study of radiographs in bronchiolitis.

Dr. Andy Willan is a senior scientist with The Research Institute at the HSC with special expertise in the design and analysis of randomized controlled trials. He has more than 20 years experience as a biostatistician and a clinical trial methodologist. He will have overall responsibility for the statistical aspects of this study.

Dr. Wendy Ungar holds an appointment of a Scientist as the Hospital for Sick Children Research Institute. She is a renowned CIHR-funded health economist with special expertise in economic analysis of asthma and bronchiolitis therapy.

Zelia Da Silva is a senior respiratory technologist at our institution with expertise in the technical aspects of oxygen saturation monitoring.
Experimental Design and Methodology

Discuss in detail the design and procedures to be used to accomplish each specific aim of the project. Describe the protocols to be used, and provide a tentative sequence or timetable for the project. Include a description of facilities and other resources and the means by which you would analyze and interpret the data. If any new methodology is to be implemented, outline its expected advantage over existing methodologies. Discuss the potential difficulties and limitations of the proposed procedures and alternative approaches to achieve the aims. Point out any procedures, situations, or materials that may be hazardous to personnel and the precautions to be taken to prevent any harm. Be complete but focused in your presentation and provide sufficient detail in the narrative to allow peer reviewers to make valid judgments regarding the quality of the project proposal. Do not exceed ten (10) pages, excluding references. Include literature references in the Literature References page provided.

Primary Research Question
In previously healthy infants 6 weeks to 12 months of age diagnosed with acute bronchiolitis in a pediatric emergency department (ED) and monitored by hourly oximetry, is the probability of hospitalization within 72 hours of arrival in those in whose oxygen saturation display is manipulated 3 percentage points above the true measurements significantly lower compared to those whose monitors display true saturations?

Secondary Research Questions - In these two groups:
A) Is there a significant difference in the probability of supplemental oxygen administration in the ED?
B) Is there a significant difference in the length of stay in the ED?
C) Is there a significant difference in the probability of unscheduled medical visits for bronchiolitis within 72 hours of commencement of the experimental intervention?
D) Is there a significant difference in the proportions of the ED physicians rating their comfort level with discharge assessed by a five point Likert scale as “very comfortable/comfortable” at 60, 120, 180, 240, 300 and 360 minutes?
E) Is there a significant association between the difference in hospitalization rate between the two groups and patient’s age, duration of symptoms, baseline saturation and clinical score?
F) What are the incremental costs/savings from the societal perspective?

Definitions
Acute Bronchiolitis
For the purposes of this study, this will consist of infants who have all of the following: coryza, cough, wheezing/crackles and tachypnea or retractions30. Only infants with their first episode of bronchiolitis will be enrolled.

Hospitalization
Hospitalization will include children who are admitted to the inpatient ward at the Hospital for Sick Children or transferred to another institution within 72 hours of presentation at the index visit or are treated in the ED during the initial visit for longer than 6 hours. Children staying for longer periods are usually admitted to hospital (see below under outcomes). Children successfully discharged will be those discharged within 6 hours with no subsequent inpatient admissions for bronchiolitis within 72 hours.

Unscheduled Medical Visit
This is defined as a subsequent visit of children initially discharged home, within 72 hours of presentation to any medical facility for bronchiolitis symptoms regardless of treatment received, or severity of illness.

Rationale for the difference in displayed saturations in the groups and for oxygen therapy in the study
Data identifying a single oxygen saturation as an ideal cut-off point for initiating oxygen therapy are lacking. The upper inflection point of the oxyhemoglobin dissociation curve is at an arterial oxygen pressure of 60mm Hg24-27, which correlates with a saturation of approximately 90%. Above and to the right of this point, the curve is relatively flat and large changes in oxygen pressure result in small changes in saturation. This characteristic of the dissociation curve supports the view that previously healthy infants with bronchiolitis and saturation at or above 90% in room air at sea level are not likely to benefit from increasing partial pressure of oxygen, especially in the absence of marked respiratory distress. This reasoning led to a recent recommendation from the AAP stating that supplemental oxygen is indicated only if saturation falls persistently below 90%27. However, the necessity of giving oxygen to infants in minimal distress whose saturations diminish to the vicinity of 90% (a common scenario, especially in sleeping infants) is not known. Many mildly distressed infants experience saturations in the vicinity of 90% without any change in their respiratory status. This population may not require inpatient admission to “improve” their oximetry values. We intend to address this issue in this study. According to the bronchiolitis study by Mallory et al19, a hypothetical saturation of 92% results in intended hospitalization rate of 83%, double of the hospitalization rate associated with saturation of 94%. Therefore, we have chosen a saturation difference of 3% between the groups which is within the instrument error27. Since this difference corresponds to a difference in the partial pressure of oxygen of only about 8mmHg, it is also of minimal physiologic importance. The physicians will be told they can choose to administer supplemental oxygen if they feel the patients’ clinical condition requires it, regardless of oxygen saturation, or according to their interpretation of the displayed
saturation. Although some physicians like to administer supplemental oxygen when the true saturation is in the low 90s the very purpose of the study is to determine if this is indeed warranted or if children with saturations in the vicinity of 90% and higher can be successfully discharged (i.e. not admitted within 72 hours).

The hypoxemia in bronchiolitis usually arises from abnormal distribution of ventilation relative to perfusion, most likely related to viral replication and inflammation1, as well as to airway reactivity and the resulting bronchospasm1,2,22. Oxygen desaturations may not be associated with increasing/severe distress. Inhaled salbutamol is associated with decreased saturations1, usually due to a transient ventilation/perfusion mismatch or due to an increase in cardiac output with a corresponding increase in oxygen requirement1.

Mild episodic hypoxia sometimes occurs in healthy infants younger than 6 months of age21 due to maturational changes of the individual components of respiratory function such as lung mechanics and functional residual capacity, cardio-respiratory rate, hemoglobin levels and sleep state14,15. The propensity to desaturate is not lost until at least 130 days of life46. Infants also show frequent desaturations in sleep13, while in their car seats14 and during air travel12-45. The British Thoracic Society suggests that desaturation to as low as 85% would have no harmful effects during airline travel12. Although this population is clearly different from that with acute respiratory compromise, there is no evidence that mild acute hypoxia in bronchiolitis heralds the danger for subsequent increase in disease severity.

**Study Design**
A randomized double-blind single center trial. In order to comply with the International Committee of Medical Journal Editors, this trial will be registered with www.clinicaltrials.gov and data collection will allow for the reporting and tracking of patients in accordance with the revised CONSORT statement for parallel group randomized trials47.

**Study population and setting**
Infants between 6 weeks and 12 months of age who present to the Emergency Department at the Hospital for Sick Children with acute bronchiolitis. The Hospital for Sick Children is a tertiary care children’s hospital in a large metropolitan city serving a catchment area of approximately five million.

**Inclusion Criteria**
1. Age 6 weeks to 12 months. Children younger than 6 weeks of age are commonly perceived to be at higher risk of deterioration than their older counterparts. Unless the disease is clearly trivial, most infants in this age group are admitted, regardless of oxygen saturation. Furthermore, in our experience most ED physicians would not be comfortable not knowing the true saturation result in extremely young infants. This age group would therefore be inappropriate to include in this study.
2. Baseline Respiratory Disease Assessment Instrument48 (RDAI) ≥ 3 points. Infants with no distress do not require saturation monitoring.
3. Informed consent.
4. Availability of a telephone.

**Exclusion Criteria**
1. True baseline oxygen saturation less than 90% in room air.
2. Prematurity less than 36 weeks gestation. This population has been found to be at an increased risk of severe bronchiolitis21,30.
3. Transfers from other institutions. These patients will have saturations documented on their transfer charts and this would bias the ED physicians’ disposition decisions.

**Sample Selection**
Children presenting when the research assistant is on duty (days and evenings) who meet the eligibility criteria will be approached for enrolment. The research assistant will keep a log of all children presenting to the ED with bronchiolitis throughout the study period whether randomized or not in order to assess the generalizability of the study. The Hospital for Sick Children is a tertiary care center, which sees the entire clinical and socio-demographic spectrum of the population. Our profile of children with bronchiolitis should therefore be comparable to that of other institutions and the generalizability of the study should not be affected and the referral bias should be minimal. A structured data collection form will be used to assess the baseline and demographic features that may affect outcome and potentially confound the comparison. This study will require the employment
of two research nurses/ respiratory therapists to enroll patients on average 10 hours a day and to run the study on average 16 hours a day (6am-midnight), 5 days a week.

**Allocation**

This process will maximize the probability of the groups to be comparable with respect to unknown or unmeasured confounding variables. Following their baseline assessment and consent, the participating infants will be randomized using a permuted block randomization scheme to the **true saturation group** undergoing hourly oximetry with true saturation values and the **altered saturation group** in which the saturation measurement display is consistently 3% above the true value. Individuals will have an equal chance of allocation to either of the two study groups. An internet-based randomization service will be used (www.randomize.net). This service has been used successfully in previous trials. The randomly allocated group assignment specifying the appropriate saturation monitor code number (corresponding to either an untouched or manipulated machine, i.e. one of the two groups) will be provided on-line to the research assistant, who will receive email confirmation. The research assistant will enter the saturation monitor code number in the confidential study logbook.

**Blinding**

In this study it is necessary to blind the ED staff, the parents and the research nurse to the group assignment by concealing the true oxygen saturation values. Although the physicians will know the displayed value, they will not know whether the measurement is true or has been altered and the clinical impact on disposition should therefore be maximized. Prior to the study, the Masimo oximeters used in the altered saturation group will be manipulated by the manufacturer so that the displayed values are consistently 3% above the true values (this will be pre-tested on a group of 20 wheezing children prior to the start of the study). The research nurse will also be blinded to the group assignment in order to minimize bias in outcome assessment and in measuring other clinical parameters. The study will have two untouched and two manipulated oximeters, each with its own ID number. The oximeters for both study groups will look identical. Only the research pharmacist and the randomization service will have the key to which ID number corresponds to which oximeter (untouched versus manipulated). For safety reasons, this key will be accessible from Zelia Da Silva or her designate if revealing this information should become necessary (extremely unlikely). To minimize the possibility of unblinding the research nurse the oximeter code assignment to the two interventions will be changed once during each bronchiolitis season and a new code list re-supplied to the randomization service and Zelia Da Silva.

**Intervention and study procedure**

Due to the 6 hour study period, reluctance of some physicians to discharge patients after midnight and parental reluctance to participate in research during the night, we shall enroll patients between 0800 and approximately 1800 hours. A study assistant on duty will screen patients for eligibility and obtain informed consent in triage. All eligible infants will have their true baseline saturation of 2% has been shown to have a potentially major impact on disposition, even though this evidence has not been proven in real practice. The ED physicians will be told that the displayed saturation may not be true and has a 50% probability of having been changed by a physiologically insignificant amount within the measurement error of the oximeter. In order to minimize the impact of any preconceived ideas regarding the significance of the 3% difference the physicians will not be told either the exact amount or the direction by which the oximeters would have been manipulated.

The research assistant will measure the respiratory rate, Respiratory Disease Assessment Instrument (RDAI) score and transcutaneous oxygen saturation at 0, 60, 120, 180, 240, 300 and 360 minutes (or at discharge time, whichever comes earlier). Oximetry of all study patients will be measured by portable oximeters which are capable of storing continuous data and graphs for up to 30 days at a set 10 second averaging time (Masimo, Irvine CA). All saturations will be measured while the infants are breathing room air for at least 2 minutes. The ED staff physician or fellow will assess all enrolled patients at these times and will estimate his/her comfort with discharge at this point, using a five point Likert scale (see outcome measures). During the study period, a concealed continuous oximetry will be done on all children in the ED to allow us to implement the safety measure of having the alarm sound should the displayed saturation drop below 88%. If this occurs the research assistant will check the probe placement since probe displacement will lead to false reading and alarms. The saturation will be re-measured and if found to be accurate the physician will be notified, supplemental oxygen will be given and the study will be discontinued. Given the entry criteria into the study, we anticipate this occurrence extremely rarely if at all.

Since the AAP bronchiolitis guidelines approve of a therapeutic trial of inhaled bronchodilators in bronchiolitis, all enrolled children will receive 1 dose of nebulized 2.5mg in 3ml normal saline and oxygen flow 8 liters per minute. This “therapeutic trial” will help minimize the variability in pharmacotherapy between the groups. The use of all medications
administered during the study protocol will be documented in order to compare co-interventions in both study groups. At the
determined whether the child can go home, their comfort with
discharged (Likert scale) and their intended use of supplemental oxygen. The research assistant will record these outcomes as
as well as the use of other therapies and investigations necessary for the economic analysis.

At discharge, all families will receive standardized discharge instructions explaining that some respiratory distress will likely
remain for another 1-2 weeks and that small frequent feeds are likely to be necessary for the next few days. These instructions
will also ask the parents to return to the ED should there be an increase in the work of breathing or poor oral intake. A study
coordinator will contact all families at 72 hours to inquire about any deterioration or hospitalization. All enrolled patients will be
advised to visit their physicians at 24-48 hours for re-assessment.

To maximize the impact of clinical assessment on disposition, we shall:

- Refrain from writing oximetry results on patients’ ED charts until the study is finished, i.e. the hospitalization is
determined. Until then, the oximetry results will be recorded in the study record only.
- Standardize the phrasing of the questions by the research assistant to the ED physician regarding disposition and
comfort related thereto in order to minimize the possibility of biased questioning.
- The oximetry measurement will be taken by the research assistant only. The saturation monitors mounted on the walls
will be turned off and all saturation probes except the one used by the research assistant will be removed from the room.
- The treating physicians of the discharged infants will not know the true saturation result. However, once the treating
physician has decided on hospitalization, a true saturation will be measured using one of the ED oximeters (not used in
the study) for the purpose of communication with the inpatient staff.

All staff in the ED will undergo education prior to the study and periodically during the study. They will be told a) the study
rationale and objectives, b) that all infants participating in this study will have true baseline saturations at least 90%, c) the
displayed saturation may or may not be true and may differ by a physiologically insignificant amount, d) should the displayed
saturation drop below an a priori defined threshold, the measurement will be verified and if accurate the study will be
discontinued and oxygen applied, e) should their patient deteriorate significantly at any time the child will be hospitalized and a
true saturation will be measured, f) supplemental oxygen should be given as per clinical indication, in conjunction with the
interpretation of the displayed saturation and g) that, to enable us to carry out the study, the ED monitors will not be used and
only the study devices will be employed. These measures should also help alleviate the ED physicians’ fear of participation by
reinforcing the safety parameters.

Unblinding Criteria

In theory, unblinding should only be used if the knowledge of the saturation is likely to/should change management or this
information is needed for communication with the inpatient staff. Prior to termination of the study, we anticipate no need for
unblinding. If the child’s respiratory status deteriorates, he/she will need to be hospitalized regardless of the oxygen saturation.
Once this decision has been made, the ED and in-patient staff will be told the true saturation and oxygen given as per usual
practice. On the other hand, provided the child is able to self hydrate and the respiratory distress is felt to be mild enough to
be compatible with discharge, revealing the saturation measurement is not justified. This will enable us to shed light on the issue if
well appearing children with saturations in the vicinity of the threshold suggested by the AAP (i.e. around 90%) can be sent
home.

Outcome Measures

Primary outcome measure will be the hospitalization for bronchiolitis within 72 hours of starting the study in the two groups.
Hospitalization will include children who are admitted to the inpatient ward at the Hospital for Sick Children, transferred to
another institution or are treated in the emergency department during the initial visit for longer than 6 hours from the start of the
study. Children staying for longer periods are usually admitted to hospital. On occasion some patients who are ultimately sent
home remain in the ED for a long time due to lack of inpatient beds. This population also consumes hospital resources and
cannot be considered discharged. Furthermore, it would be impractical to maintain the blinding beyond 6 hours.
Hospitalizations occurring subsequently will be identified during the telephone follow-ups.

This outcome incorporates both the short term disposition and safety. Children going home within 6 hours who do not require
subsequent hospitalization within 72 hours can be considered successfully discharged. Vast majority of patients who do require
subsequent admission to hospital return within 72 hours. Hospitalizations after 72 hours are likely to be related to the
progression of the disease and may have little relationship to the status at the index visit.

Unscheduled medical visits are not a good reflection of safety since most require reassurance/education only and do not result in
major outcomes such as hospitalization. Although ICU admissions/ventilations for bronchiolitis do represent a major safety
aspect, we do not expect this outcome to happen, given our entry criteria. However, this information will be collected (see Other
outcomes below).
Hospital admission can be a very stressful event for both caregivers and infants. It also impacts on the rest of the family since caregivers often have to take time off work and arrange alternative sources of care for the other children. Hospitalization may also have a major financial impact on the family and the health care system. Economic evaluations have indicated that the major societal cost associated with RSV related lower respiratory tract infections is hospitalization.  

Some physicians have expressed concerns regarding the remote possibility of future adverse neurobehavioral outcomes in children with history of hypoxia. The published evidence regarding potential association between hypoxia in asthma and adverse outcomes is inconsistent, and has not been shown to be causative. Overwhelming majority of children quoted in the literature were not previously healthy, but suffered from severe congenital heart disease or chronic sleep disorders rendering them susceptible to a chronic hypoxic insult. This population was, therefore, very different from the one we want to study. We feel it unlikely that the range of mild hypoxia expected to last for a very limited time period as is the case in our study would by itself cause future adverse neurobehavioral effects. Since this long-term outcome is clearly unrealistic to examine in this study, we could not incorporate it as a measure of safety.

**Secondary outcome measures** - The two groups will also be compared with respect to the following:

- The proportions of infants receiving supplemental oxygen in the ED.
- Length of stay in the ED (from the time of arrival to the disposition decision).
- Proportions of infants with unscheduled medical visits for bronchiolitis symptoms to any medical facility within 72 hours of the start of the study.
- Association between the primary outcome (hospitalization) in the two groups and patients’ age, duration of respiratory distress, baseline RDAI, and baseline saturation.
- Proportion of the ED staff/ fellows’ “strong agreement” or “agreement” with discharge at 0, 60, 120, 180, 240, 300 and 360 minutes. They will be asked the following question “Based on this infant’s clinical appearance, degree of respiratory distress, hydration status, vital signs and oxygen saturation, he/she is ready for discharge at this point in time”:
  - Strongly agree
  - Agree
  - Neither agree nor disagree
  - Disagree
  - Strongly disagree
- The incremental costs of the true saturation group compared to the altered saturation group from the societal perspective.

**Other outcomes**

Admission to ICU/ventilation within 72 hours. These outcomes are extremely rare and highly unlikely to occur given our inclusion/exclusion criteria. Realistically, the study cannot be powered for a meaningful statistical analysis using this outcome. However, if it does occur, the study results will be interpreted accordingly.

**Study Implementation**

Prior to the study, emergency department staff physicians and fellows and emergency nurses will be educated regarding all components of the study. Particular attention will be paid to the rationale and importance of concealing the saturation and implementation of the safety measures. The research coordinator and the study assistants will also be trained in all aspects of the study execution, including obtaining informed consent, technical aspects of valid oximetry measurements and the RDAI. Also, the manipulated oximeters will be pre-tested on a cohort of 20 children with acute respiratory distress to ensure accurate 3% difference compared to the oximeters with true measurements.

This study requires the following personnel:

1. **Research coordinator** – this individual will supervise the research assistants, communicate with the primary investigator, organize follow-up telephone calls, oversee the budget and organize the study log of all infants 12 months of age and younger presenting with bronchiolitis to the ED within the recruitment period.

2. **Research assistants** – this will consist of two senior research nurses or respiratory therapists with extensive prior nursing and research experience who will be trained and responsible for screening, enrollment, study execution and use of the data collection forms.

**Follow-up phone calls**

All infants enrolled in the study will receive a phone call from a research coordinator approximately 72 hours after discharge from the index visit to determine subsequent medical visits or hospitalizations for bronchiolitis. If unsuccessful, calls will be made twice a day until day 7. This approach has resulted in 99% success follow-up rate in our recent bronchiolitis study. The follow-up phone calls will be made by a study coordinator who will be blinded to treatment allocation. The CIHI/OHIP/NACRS databases will also be searched to ascertain further use of health care resources within 72 hours of discharge.
Sample Size

The logs of our previous bronchiolitis studies as well as the literature suggest that approximately 30% of children with bronchiolitis are hospitalized\textsuperscript{a}, or stay in the ED beyond 6 hours.

This calculation is based on the assessment of the between-group difference in proportions of hospitalizations. This is a superiority study in which the adoption of the interventional monitoring criteria can only be recommended for future practice if the rate of the primary outcome in this group is significantly lower than in the controls. The null hypothesis for the primary analysis is that the probability of hospitalization in the altered saturation arm is no less than the probability of hospitalization in the true saturation arm. That is, $H_0: \pi_1 - \pi_0 \geq 0$, where $\pi_0$ and $\pi_1$ are the probability of hospitalization in the altered saturation and true saturation arms, respectively. The specific alternative hypothesis for which we wish to have sufficient power is that the hospitalization rate in the altered saturation arm is lower by at least 15 percentage points, that is $H_1: \pi_1 - \pi_0 \leq -0.15$. A discussion among the investigators and the ED physicians revealed that if the difference is of this magnitude adopting the interventional monitoring practice would be preferred. This target difference is also in agreement with the reported 2.5 fold increase in admission rates since routine oximetry monitoring had been adopted. For a one-sided test to have a type I error of 0.05 and a power of 80%, we need to randomize 108 patients per arm, for a total of 216\textsuperscript{b}. To be conservative, we assume a refusal rate of 10% and a dropout rate of 5%. Therefore, we plan to approach 254 patients in order to randomize 228 and have complete data on 216.

Analysis

Baseline variables:
Baseline characteristics such as age, duration of respiratory distress, respiratory rate and oxygen saturation at randomization will be compared between the two groups using the appropriate descriptive statistics. Frequency counts and percentages will be given for discreet variables and means, medians, standard deviations and interquartile ranges for continuous variables. Baseline characteristics will be analyzed to determine if there is a need to adjust for any significant differences between the study groups.

The primary analysis will be performed using a one-sided Fisher’s exact test at the 5% level. A one-sided test for the primary analysis is proposed since we need only limit the probability of erroneously concluding altered saturation group has fewer hospitalizations since that would argue for deemphasizing the saturation measurements and have disposition decided on primarily clinical basis. To observe that the altered saturation group is equal or inferior to the true saturation group, whether the difference was significant or not, would argue for not changing current practice.

An intention to treat analysis will be used with all randomized participants included in the analysis as part of the groups to which they were randomized regardless of whether they completed the study or not. The rare patient for whom the hospitalization status is not known cannot be included.

The secondary analyses will include:

a) Fisher’s Exact Test will be used to compare the proportions of children receiving supplemental oxygen in the ED during the study in the two groups.

b) A Mann-Whitney U test will be used to compare treatment arms with respect to length of stay in the ED.

c) Fisher’s exact test will be used to compare the proportions of children with unscheduled medical visits within 72 hours of the index visit.

d) Fisher’s exact test will be used to compare the proportions of physicians agreeing/ strongly agreeing with discharge at each time.

e) Logistic regression analysis will be used to determine association between the difference in the primary outcome while controlling for age, baseline saturation, RDAI, respiratory rate.

f) Economic analysis

The statistical tests of hypotheses for the secondary outcomes a) through g) will be set at the 0.01 level to account for the issue of multiple testing and to maintain an overall type I error of 0.05.

Economic Analysis

The objective of the economic evaluation is to assess the incremental costs/ savings of using the two interventional study strategies of infants presenting with acute bronchiolitis, by examining costs and consequences. This study design will enable the capture of real world cost data, which is essential for incorporating economic evaluation into budget allocation decisions. The results will be expressed as the incremental cost (or savings) of deemphasizing pulse oximetry and making the disposition decision primarily clinically driven, provided the saturation remains within the safety limits outlined in the study. The economic evaluation will be assessed from the perspective of society, including public (provincially paid for) health care system costs, private out-of-pocket costs and parental time losses. The time horizon for the full analysis will be 72 hours in accordance with the primary study objective of examining the probability of admission.

The direct health care resource costs associated with each treatment arm consist of professional services (physicians,
Only the resource use related to the infant's acute bronchiolitis episode within the first 72 hours will be included in the economic analysis. This includes health care provided due to the infant's condition, due to the administration of interventions or due to adverse events related to the interventions. During the cost evaluation, prices will be assigned to each health resource item, with the exception of out-of-pocket expenses, time losses and wages which will be supplied by the parent directly. Prices will be derived from physician fee schedules, the Ontario Drug Benefits formulary, equipment wholesaler price lists and other sources. Overhead costs of ED and inpatient services and costs of resources consumed in the ED and on inpatient wards will be obtained by departmental micro-costing. Given that some costs may be incurred by the parent and some by the child, all costs will be assigned to the child as the unit of analysis. The volume of resource use and unit price of each cost item will be presented separately. This will facilitate comparisons with other studies as well as other countries. In addition, cost items will be aggregated according to the major cost categories.

The primary clinical endpoint of hospital admissions will be incorporated into the cost analysis and will therefore not be used as a surrogate marker for effectiveness. A cost consequence analysis will be undertaken that will represent the costs as well as the hospital admission rates in the true saturation group and the altered saturation group.

Sensitivity analysis will be used to test the robustness of the result to variations in the underlying assumptions. The variables that will be varied in one-way and multi-way sensitivity analyses include the outcome measure (hospitalization within 72 hours) and the most costly health resource items, e.g. Emergency Department nursing time costs and inpatient care. As some of the nursing time may be protocol driven, varying this item will allow for extrapolation of findings to non-research settings. The impact of modifying the values of other variables, such as the prices of specific resources, may also be investigated.

Feasibility

We plan to execute the study on average 16 hours a day and to enroll new patients on average 10 hours a day, with the intervention lasting 6 hours. Bronchiolitis cases usually occur between December and April and thus we plan to recruit children during these months. Our past bronchiolitis logs indicate that approximately 500 infants with bronchiolitis present to our ED during each winter season, 400 of whom present without severe disease and with saturations ≥ 90%. Assuming that 25% will meet our inclusion criteria, 88 infants will be available for enrollment 10 hours a day 5 days a week during each winter season. A discussion among the investigators based on experience and review of the logs of past bronchiolitis studies concluded that a brief study like this is unlikely to have a drop-out rate greater than 5%, a refusal rate greater than 10% and a miss rate greater than 5%. Approximately 76 consents and 72 patients with complete data are therefore anticipated each season. We anticipate that it will take us 51 weeks (3 bronchiolitis seasons) to accrue the necessary sample size.

Prior to writing this proposal, we have informally surveyed our ED colleagues, requesting their opinion about anticipated problems related to this issue. They appear overwhelmingly supportive. Furthermore, as mentioned in the protocol, we plan an extensive educational endeavor before and during the study, emphasizing the need for blinding the true saturations, and various safety aspects of the study.

Safety Measures –

A) Data Safety Monitoring Committee & Interim Analysis

This will consist of a biostatistician not involved in the study, a respiratory specialist and an ED attending physician. They will meet after the initial 100 patients have been enrolled in order to review the results of the interim analysis. Since this analysis is for safety purposes and no analysis of the primary or secondary outcomes will be performed, sample size adjustment and stopping rules are not required. To ensure safety of the participating subjects, there will be one planned interim analysis on the first 100 patients randomized. The interim analyses will test the hypothesis $H_0: \pi_\text{true} = \pi_\text{alter} \geq 0$, versus $H_1: \pi_\text{true} > \pi_\text{alter} < 0$ where $\pi_\text{true}$ and $\pi_\text{alter}$ are the probability of hospitalization in the altered saturation and true saturation arms, respectively. That is, we are looking for evidence that the probability of hospitalization in the altered saturation arm is higher than in the true saturation arm and we will stop the trial in favour of the true saturation arm if $H_0$ is rejected at the one-sided 5% level. The interim analysis is meant to protect against the possibility that altered saturations (i.e. deemphasizing saturation measurements) produces more hospitalizations. Since $H_0$ and $H_1: \pi_\text{true} = \pi_\text{alter} \leq 0$ (the null hypothesis for the final analysis) are different hypotheses, testing $H_0$ will not increase the probability of rejecting $H$ erroneously, that is, testing $H_0$ will not increase the type I error associated with the final analysis.

In addition to the interim analysis, the Data Safety Monitoring Committee will meet once during each bronchiolitis season to discuss any significant concerns raised by the investigators and the research coordinators. Furthermore, their will be ad hoc meetings should any cases of ICU admissions or ventilation within 72 hours arise. The DSMC will review these cases in detail and decide if any action needs to be taken. The PI will contact the DSMC within 48 hours of obtaining information of all emergency unblinding (see also Adverse events).

B) Adverse Events & Safety of the participants

The precise oxygen saturation associated with acute respiratory compromise which results in adverse effects is not known. However, this point lies well below the range of saturations which will occur in our study. The degree of hypoxia which will
happen in our patient population can be expected to result in no adverse effects. High risk population such as infants with low cardiac output, sepsis or other system derangement necessitating normal oxygen saturation will be excluded. Children with chronic hypoxia which may result in pulmonary hypertension will not participate either.

In this study, to maximize the safety of the participants, infants with saturations <90% and those in severe respiratory distress at presentation will be excluded. This will minimize the probability of subsequent significant desaturations and major deterioration. All enrolled infants will be monitored hourly by both the research nurse and the ED physicians. Should the status of any patient deteriorate significantly, he/she will be admitted and appropriate therapy instituted. Safety alarms are not normally used during intermittent oximetry. However, as an additional safety measure we have instituted continuous oximetry monitoring with a safety alarm to sound should the displayed saturation drop below 88%. Additionally, should the true saturation drop below 87%, the alarm will sound and appropriate measures instituted. The oxygen saturation threshold for study entry and for commencing supplemental oxygen is in close proximity to that quoted in the recently published AAP guidelines on bronchiolitis management.

The main adverse events which will be documented and reported in the manuscript will be the children requiring ventilation and those requiring ICU care within 72 hours of the initial discharge. These events will also be considered serious, mandating their reporting to the Research Ethics Board within 48 hours.

**Divisional support for the study**

This study demands extensive ongoing education of the ED physicians and nurses in the necessity of the binding of the true oxygen saturations, implementation and maintenance of the blinding strategies as well as our goal to use oximetry efficiently and interpret its results appropriately. For some staff who currently place great importance on oximetry this study will represent a significant departure from usual practice. Dr. William Mounstephen, our Divisional Director and Dr. Bruce Minnes, our Associate Clinical Director, both support the importance of this study and are prepared to assist with its implementation.

**Dissemination of Results and Future Directions**

The results of this study will be submitted for presentation at either the annual meeting of the Pediatric Academic Society, the Society for Academic Emergency Medicine or the American Academy of Pediatrics. We shall also submit the manuscript for publication in a peer reviewed scientific journal. Future studies will need to address the impact of oximetry on the hospitalized patients with bronchiolitis.

**Limitations**

It is possible that not knowing the true saturation may make the ED physicians more cautious than usual and that more patients may be admitted as a result. However, this is equally likely to occur in both study arms and should not contribute to the difference in primary outcome between the groups.

Since the research nurse will measure the true screening saturations it is possible that he/she may become unblended upon subsequently using the study oximeters. However, this probability is not large since saturations frequently vary by several percent over a period of several minutes that it will take the nurse to start the study.

It is quite likely that the number of patients with true saturations below 90% will be relatively small and the power to make firm conclusions about the probability of successful discharge at each saturation level below this threshold may be limited.

The duration of blinding of oxygen saturation will be limited to 6 hours since beyond this point the patients are deemed admitted. The question of the impact of oximetry on inpatient stay has been retrospectively explored, and needs to be investigated prospectively in a separate study.


22. Roback MG, Baskin MN. Failure of oxygen saturation and clinical assessment to predict which patients with bronchiolitis discharged from the emergency department will return requiring admission. Pediatric emergency care 1997;13:9-11.


37. Lenard HG. The development of sleep spindles in the EEG during the first two years of life. Neuropadiatrie 1970;1:264-76.


Principal Investigator: Suzanne Schuh

**Collaborative Arrangements**

Provide a detailed explanation of any project-related programmatic, financial, and administrative arrangements made between the Supervising Institution and any collaborating organizations. Furnish letters confirming the agreement between the Supervising Institution and any collaborating organization.

None required.
International Activities

If the project will be conducted outside the United States at any time, you must give a complete explanation of international involvement. Document and include project endorsements by foreign governments if any are required in the setting in which the work is being carried out.

All project activity will occur at the Hospital for Sick Children, Toronto, ON, Canada since this is the institutional affiliation of all investigators related to this project. No foreign government endorsement is required for this project.
### Detailed Budget for First 12-Month Budget Period

(Expand the cells in the itemized sections as necessary, but limit total space to one page)

<table>
<thead>
<tr>
<th>Name</th>
<th>Project position title</th>
<th>Time/Effort</th>
<th>US $ Amount Requested (Omit cents)</th>
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<tr>
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<td>Stephen Freedman, Allan Coates, Patricia Parkin, Upton Allen, Andrew Willan, Wendy Ungar, Zelia DaSilva</td>
<td>Co-Investigators</td>
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<td>Biljana Klasninovska</td>
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Subtotal of personnel costs: 77779

### Consultant(s) Costs

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Subtotal of consultant costs:

| Supplies (itemize, expand any boxes as needed) | Supplies (continued) |
| Paper | Photocopying | File Folders | Binders |
| Domestic travel (itemize) | Domestic travel (continued) |
| Foreign travel (itemize) | Foreign travel (continued) |
| Patient care costs (itemize) | Patient care costs (continued) |
| Other expenses (itemize) | Other expenses (continued) |
| Technical aspects of blinding | Internet Randomization Service |
|                                  | Subtotal = 2250 |

Indirect costs-Supervising Institution (not to exceed 7 percent of the above subtotals) Subtotal = 5665

| Equipment (itemize) | Equipment (continued) |
| 4 Oximeters (Masimo) | 12600 + |
| Technical costs for blinding oximeters | 2550 + |
| 240 probes | 4100 = 19250 |

Contractual Costs (itemize on the following page, and enter the total as the subtotal on this line.) Subtotal =

Total First Year Budget = 105844
### Contractual Costs for First 12-Month Budget Period

**Principal Investigator**: Suzanne Schuh

#### Personnel

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**Subtotal of personnel costs**: 0

#### Consultant(s) Costs

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**Subtotal of consultant costs**: 0

#### Supplies (itemize, expand any boxes as needed)

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**Subtotal of supplies**: 0

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**Subtotal of domestic travel**: 0

#### Foreign travel (itemize)

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**Subtotal of foreign travel**: 0

#### Patient care costs (itemize)

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**Subtotal of patient care costs**: 0

#### Other expenses (itemize)

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**Subtotal of other expenses**: 0

#### Indirect costs-Contractual Institution (not to exceed 7 percent of the above subtotals)

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**Subtotal of equipment**: 0

**Total**: 0

*(Enter this total as the first year contractual costs Subtotal on the Detailed Budget for First 12-Month Budget page)*
### Detailed Budget for Second 12-Month Budget Period

(Expand the cells in the itemized sections as necessary, but limit total space to one page)

#### Personnel

<table>
<thead>
<tr>
<th>Name</th>
<th>Project position title</th>
<th>Time/Effort</th>
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<tr>
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<td>Co-Investigators</td>
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Subtotal of personnel costs: **78817**

#### Consultant(s) Costs

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Subtotal of consultant costs: **Subtotal**

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Indirect costs-Supervising Institution (not to exceed 7 percent of the above subtotals)

**Subtotal** **5518**

#### Equipment

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Contractual Costs (Itemize on the following page, and enter the total as the subtotal on this line.)

**Subtotal** **Subtotal**

**Total Second Year Budget** **84335**
### Contractual Costs for Second 12-Month Budget Period

(Limit to one page)

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**Subtotal of personnel costs**

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<tr>
<th>Consultant(s) Costs</th>
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<tbody>
<tr>
<td>Name</td>
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**Subtotal of consultant costs**

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<table>
<thead>
<tr>
<th>Supplies (itemize, expand any boxes as needed)</th>
<th>Supplies (continued)</th>
</tr>
</thead>
<tbody>
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**Subtotal**

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**Subtotal**

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<thead>
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<th>Foreign travel (itemize)</th>
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**Subtotal**

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<table>
<thead>
<tr>
<th>Patient care costs (itemize)</th>
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**Subtotal**

0

<table>
<thead>
<tr>
<th>Other expenses (itemize)</th>
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</table>

**Subtotal**

0

<table>
<thead>
<tr>
<th>Indirect costs-Contractual Institution (not to exceed 7 percent of the above subtotals)</th>
</tr>
</thead>
<tbody>
<tr>
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</table>

**Subtotal**

0

<table>
<thead>
<tr>
<th>Equipment (itemize)</th>
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</tbody>
</table>

**Subtotal**

0

(Enter this total as the second year contractual costs Subtotal on the Detailed Budget for Second 12-Month Budget page)

**Total**

0
### Detailed Budget for Third 12-Month Budget Period
(Expand the cells in the itemized sections as necessary, but limit total space to one page)

#### Personnel

<table>
<thead>
<tr>
<th>Name</th>
<th>Project position title</th>
<th>%</th>
<th>Hours per week</th>
<th>US $ Amount Requested (Omit cents)</th>
<th>Fringe benefits</th>
<th>Salary + Fringe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suzanne Schuh</td>
<td>Principal Investigator</td>
<td>20</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Stephen Freedman, Allan Coates, Patricia Parkin, Upton Allen, Andrew Willan, Wendy Ungar, Zelia DaSilva</td>
<td>Co-Investigators</td>
<td>2 each</td>
<td>1 each</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Research Coordinator</td>
<td></td>
<td>25</td>
<td>10</td>
<td>8464</td>
<td>1947</td>
<td>10415</td>
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<tr>
<td>Research Assistant</td>
<td></td>
<td>100</td>
<td>37.5</td>
<td>28935</td>
<td>6655</td>
<td>35590</td>
</tr>
</tbody>
</table>

Subtotal of personnel costs: 81591

#### Consultant(s) Costs

<table>
<thead>
<tr>
<th>Name</th>
<th>Institutional affiliation</th>
<th>Salary</th>
<th>Fringe benefits</th>
<th>Salary + Fringe</th>
</tr>
</thead>
</table>

Subtotal of consultant costs: 0

#### Supplies

<table>
<thead>
<tr>
<th>Description</th>
<th>US $ Amount Requested (Omit cents)</th>
<th>Fringe benefits</th>
<th>Salary + Fringe</th>
</tr>
</thead>
</table>

Subtotal: Supplies (continued)

#### Domestic travel

<table>
<thead>
<tr>
<th>Description</th>
<th>US $ Amount Requested (Omit cents)</th>
<th>Fringe benefits</th>
<th>Salary + Fringe</th>
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</table>

Subtotal: Domestic travel (continued)

#### Foreign travel

<table>
<thead>
<tr>
<th>Description</th>
<th>US $ Amount Requested (Omit cents)</th>
<th>Fringe benefits</th>
<th>Salary + Fringe</th>
</tr>
</thead>
</table>

Subtotal: Travel to a Scientific Meeting to present results

Patient care costs

<table>
<thead>
<tr>
<th>Description</th>
<th>US $ Amount Requested (Omit cents)</th>
<th>Fringe benefits</th>
<th>Salary + Fringe</th>
</tr>
</thead>
</table>

Subtotal: Patient care costs (continued)

Other expenses

<table>
<thead>
<tr>
<th>Description</th>
<th>US $ Amount Requested (Omit cents)</th>
<th>Fringe benefits</th>
<th>Salary + Fringe</th>
</tr>
</thead>
</table>

Subtotal: Other expenses (continued)

Statistical data management at $45 US/hr x 100 hrs
Economic Analysis at $45 US/hr x 100 hrs
Reprints: $552

Subtotal: 11622

Indirect costs-Supervising Institution (not to exceed 7 percent of the above subtotals)

Subtotal: 6644

Equipment

<table>
<thead>
<tr>
<th>Description</th>
<th>US $ Amount Requested (Omit cents)</th>
<th>Fringe benefits</th>
<th>Salary + Fringe</th>
</tr>
</thead>
</table>

Subtotal: Equipment (continued)

Total Contractual Costs

Subtotal: 101557

Total Third Year Budget: 101557
## Contractual Costs for Third 12-Month Budget Period

**Personnel**

<table>
<thead>
<tr>
<th>Name</th>
<th>Project position title</th>
<th>%</th>
<th>Hours per week</th>
<th>Salary</th>
<th>Fringe benefits</th>
<th>Salary + Fringe</th>
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**Subtotal of personnel costs**

0

**Consultant(s) Costs**

<table>
<thead>
<tr>
<th>Name</th>
<th>Institutional affiliation</th>
<th>Salary</th>
<th>Fringe benefits</th>
<th>Salary + Fringe</th>
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</tbody>
</table>

**Subtotal of consultant costs**

0

- **Supplies (itemize, expand any boxes as needed)**
  - Supplies (continued)
    - **Subtotal**

- **Domestic travel (itemize)**
  - Domestic travel (continued)
    - **Subtotal**

- **Foreign travel (itemize)**
  - Foreign travel (continued)
    - **Subtotal**

- **Patient care costs (itemize)**
  - Patient care costs (continued)
    - **Subtotal**

- **Other expenses (itemize)**
  - Other expenses (continued)
    - **Subtotal**

- **Indirect costs-Contractual Institution (not to exceed 7 percent of the above subtotals)**
  - **Subtotal**

- **Equipment (itemize)**
  - Equipment (continued)
    - **Subtotal**

(Enter this total as the third year contractual costs Subtotal on the Detailed Budget for Third 12-Month Budget page) **Total**

0
Principal Investigator: Suzanne Schuh

### Budget for Entire Proposed Project

<table>
<thead>
<tr>
<th>Budget category totals</th>
<th>First Budget Period</th>
<th>Second Budget Period</th>
<th>Third Budget Period</th>
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</thead>
<tbody>
<tr>
<td>Personnel costs</td>
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<td>78817</td>
<td>81591</td>
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<tr>
<td>Consultant costs</td>
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<tr>
<td>Supplies</td>
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<td>Other expenses</td>
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<td>Travel</td>
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<td>Patient care costs</td>
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<tr>
<td>Indirect costs - supervising institution</td>
<td>5665</td>
<td>5518</td>
<td>6644</td>
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<tr>
<td>Equipment</td>
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<td>Contractual costs</td>
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<tr>
<td><strong>Subtotal by year</strong></td>
<td>105844</td>
<td>84335</td>
<td>101557</td>
</tr>
</tbody>
</table>

**Total for entire proposed project** (Also write this amount on page 1) $291,736 USD (Already funded for $163,000 CND)

### Justification for the budget:

#### Investigators

The study investigators do not require any salary support.

#### Clinical Research Coordinator

This individual will be a senior nurse/respiratory therapist who will be responsible for the following:

1. Communication with research assistants, scheduling and organizing payroll.
2. Promoting the study within the emergency department, telephone follow-ups.
3. Liaison with principle investigator regarding any study concerns.
5. Study log of all patients with bronchiolitis presenting to the ED and those who were not enrolled due to absence from duty, due to exclusion criteria, refusal to participate and missed patients.
6. Data abstraction into the database, dissemination of the results, participation in manuscript preparation.

We anticipate these duties will take approximately 10 hours per week. The study will take place for 21 weeks during each winter season (December through April) but the research coordinator will work for 1 week prior to and 1 week post study during each season in order to attend to various administrative study related details. The current hourly rate for a senior research nurse includes a base rate of $36.82 Canadian dollars per hour plus 23% fringe benefits. Assuming the study will start in 1 year, this rate will increase by 3.5% per year (institutional requirement) and the calculated hourly rate is therefore $38.10 Canadian dollars per hour or $34.30 US dollars per hour (depending on the exchange rate) plus 23% benefits for the first year. Factoring in an annual 3.5% increase raises the baseline hourly rate to $35.50 US per hour and $36.80 US per hour for the second and third year of the study, respectively.

#### Research Nurse/ Respiratory Therapist

This study requires hiring two full-time research assistants who will be trained by the principal investigator and involved in eligibility assessment, patient enrollment, randomization, use of patient data form, patient monitoring and outcome data assessment during the study, as well as ensuring that the ED staff looking after patients is blinded to true oxygen saturations. Since they will also measure the clinical score, vital signs, and have to recognize any changes in the respiratory status in a timely fashion, these
individuals will be senior pediatric research nurses with previous nursing and research experience. Our extensive experience confirms the absolute necessity for a dedicated research assistant present on the premises. The busy ED staff cannot be expected to contact the research nurse in a timely fashion and any recruitment relying on calling a nurse on call would therefore compromise enrollment.

Since the interventional period will last approximately 6 hours, we shall enroll patients from 8 AM to 6 PM and execute the study until approximately midnight. The bronchiolitis season extends from early December through April and the study will therefore run for 21 weeks during each winter season. The salary for the research assistants (nurses) will be $34.30 US per hour plus 23% fringe benefits (mandated by the institution) and will increase 3.5% per year thereafter. This rate is based on the hourly rate of a senior nurse working in the Hospital for Sick Children. We anticipate the study will require enrollment during three 21-week winter seasons for a total of 63 weeks of employment.

**Database Development**
Consultation with the Hospital for Sick Children Research Institute database development staff provided an estimate of 40 hours required at a rate of $33.10 US per hour plus 23% fringe benefits.

**Internet Randomization Service**
A standard fee for this service is $2500 Canadian or approximately $2250 US dollars.

**Statistical Analysis**
This study will require an extensive statistical analysis. Dr. Andy Willan will closely supervise his statistical staff. He estimates this process will require 100 hours at a standard fee of $50.00 Canadian an hour ($45.00 US) plus 23% fringe benefits.

**Economic Analysis**
This study will require an extensive statistical analysis. Dr. Wendy Ungar will closely supervise her staff to complete this task. She estimates this process will require 100 hours at a standard fee of $50.00 Canadian an hour ($45.00 US) plus 23% fringe benefits.

**Equipment**
Since we anticipate enrolling more than one child at the same time, we intend to purchase 4 portable oximeters, at a cost of $3150US each. This price is directly quoted from the manufacturer. To manipulate two oximeters for blinding purposes will cost approximately $1275US per monitor. We also need to buy 240 oximeter probes at a cost of $17US per probe.

**Travel**
The results of this study will be submitted for presentation at a scientific meeting and a budget to cover the cost of the conference is therefore requested.

**Publication Costs**
The fee for reprints of the published manuscript is included in this budget.
Principal Investigator: Suzanne Schuh

Other Support

For each of the professionals named on the budget pages, list the title, start and end dates, source of funding, and yearly amounts of all state, federal, commercial, and private funding support. Include this information for active grants, proposals under review, and proposals being prepared for submission. Indicate the percentage of effort for investigators in each project.

Suzanne Schuh, MD, FRCPC, FAAP (PEM)
Staff Pediatrician and Research Director, Emergency Department
Senior Associate Scientist, Research Institute
The Hospital for Sick Children
Professor of Pediatrics, University of Toronto
Start Date: January 1, 1985
End Date: None
Source of funding: PSI, HSC Foundation, Merck Frosst Canada, Trudell Medical
Annual state/federal/commercial/private support: None

Current Support for this Study:
Impact of Oximetry on Hospitalization in Acute Bronchiolitis.
Funded by Physicians’ Services Incorporated Foundation March 2007 for $163,000 CND

Active grants:
1. Emergency Department Rapid Intravenous Rehydration (RIVR) for Pediatric Gastroenteritis: A Randomized Controlled Trial
Physicians’ Services Incorporated ($165,000 2006 - 2008)
Percentage of Effort: 10% involvement

2. Predictors for Diagnostically Accurate Ultrasound in Children with Suspected Appendicitis.
HSC Foundation ($128,000 2007 - 2009)
Percentage of Effort: 20% involvement

3. Can Montelukast Shorten Corticosteroid Therapy in Children with Mild to Moderate Acute Asthma?
Merck Frosst Canada ($314,414 2005 - 2007)
Percentage of Effort: 30% involvement

4. Funding for research Coordinator Initiative spearheaded by S. Schuh, the Research Director in the ED.
Trudell Medical ($50,000 2006 - 2008)
Percentage of Effort: 5% involvement

Proposals under review:
1. Can Young Infants with Acute Wheezing be Stabilized With Salbutamol By Metered Dose Inhalers?
Submitted to HSC Foundation October 2006
Percentage of Effort on grant: 80% involvement

2. Efficacy of Cold Air in the Treatment of Croup.
Submitted to Physicians’ Services Incorporated Foundation February 2007
Percentage of Effort on grant: 30% involvement

Submitted to Physicians’ Services Incorporated Foundation November 2006
Percentage of Effort on grant: 10% involvement

Submitted to HSC Foundation October 2006
Percentage of Effort on grant: 10% involvement

Proposals being prepared for submission: None

Stephen B. Freedman, MDCM, MSCI, FAAP, FRCP(C)
Staff Pediatrician, Emergency Department
The Hospital for Sick Children
Assistant Professor of Pediatrics, University of Toronto
Start Date: October 15, 2004
End Date: None
Source of funding: Pediatric Consultants & Physician’s Services Incorporated
Annual state/federal/commercial/private support: None
Active grants:
1. The Impact of an Emergency Department and Community Based Gastroenteritis Protocol on Knowledge and Emergency Department Utilization.
   Pediatric Consultants Educational Research Grant ($4,527 2005)
   Percentage of Effort: 80% involvement

2. Emergency Department Rapid Intravenous Rehydration for Pediatric Gastroenteritis: A Randomized Controlled Trial.
   Physician Services Incorporated Foundation ($156,000 2005 - 2007)
   Percentage of Effort: 80% involvement

Proposals under review:
- Isotonic versus hypotonic IV maintenance fluids in children: a randomized controlled trial.
  Submitted to Paediatric Consultants Creative Professional Activity Grant March 2007
  Percent of effort on Grant: 20%

Proposals being prepared for submission:
- The role of Probiotics in Gastroenteritis in a Pediatric Emergency Department

Allan Coates, MD, CM
Staff Physician
Division of Respiratory Medicine
The Hospital for Sick Children
Professor of Pediatrics, University of Toronto
Start Date: January 1, 1997
End Date: None
Source of funding: Canadian Cystic Fibrosis Foundation & CIHR
Annual state/federal/commercial/private support: None
Active grants:
1. The impact of habitual physical activity on disease progression in cystic fibrosis.
   Canadian Cystic Fibrosis Foundation (2003-2006 $232,923; 2006-2008 $180,000)
   Percentage of Effort: 20% involvement

2. Training Program in Clinical Nutrition
   Canadian Institutes of Health Research (CIHR) Grant (2002-2008 $1,590,000)
   Percentage of Effort: 10% involvement
Proposals under review: None
Proposals being prepared for submission: None

Patricia Parkin, MD, FRCP(C)
Staff Physician
Division of Pediatric Medicine
The Hospital for Sick Children
Assistant Professor of Pediatrics, University of Toronto
Start Date: July 1, 1988
End Date: None
Source of funding: University of Toronto, Hospital for Sick Children Foundation, Danone Institute, PSI, Sanofi, Heart and Stroke Foundation,
Annual state/federal/commercial/private support: None
Active grants:
1. Treatment choices for children with typical acute immune thrombocytopenic purpura: development of a decision aid.
   University of Toronto (2006-2011 $10,000)
   Percentage of Effort: 30%

2. Palindromy at the NF1 locus as a risk factor for NF1-associated malignancy
   Hospital for Sick Children (2006-2009 $45,023)
   Percentage of Effort: 30%
3. Nutritional education and the prevention of iron depletion in children 9 months to 2 years: a randomized trial  
Danone Institute (2006-2008 $61,148)  
Percentage of Effort: 70%

4. Emergency Department rapid intravenous rehydration for pediatric gastroenteritis: a randomized controlled trial  
Physicians Services Incorporated Foundation (2006-2008 $156,000)  
Percentage of Effort: 10%

5. Does the order in which vaccines are administered affect pain response? A randomized, double-blind, clinical trial of Pentacel vs Prevnar  
Sanofi (2006-2007 $17,250)  
Percentage of Effort: 10%

6. An office based intervention to improve media use in preschool children: a randomized controlled trial  
Hospital for Sick Children (2006-2007 $9,975)  
Percentage of Effort: 30%

7. Modifiable risk factors for acute chest syndrome in children with sickle cell disease admitted to hospital with a painful crisis  
Hospital for Sick Children (2005-2007 $3,750)  
Percentage of Effort: 30%

8. PEWS translation project: from retrospective algorithm to real-time bedside tool  
Heart and Stroke Foundation (2006-2007 $74,652)  
Percentage of Effort: 10%

Proposals under review: None  
Proposals being prepared for submission: None

Upton Allen, MBBS, MSc, FAAP, FRCP(C)  
Director of Infectious Diseases  
The Hospital for Sick Children  
Professor of Pediatrics, University of Toronto  
Start Date: April 1995  
End Date: None  
Source of funding:

1. Prospective cohort study of genetic variation and risk of infection in Canadian children with primary acute myeloid leukemia.  
National Cancer Institutes of Canada ($444,424, 2005-2008)  
Percentage of Effort: 15% involvement

2. Immunogenicity of 7-valent pneumococcal conjugate vaccine in HIV-infected children.  
Physicians Services Incorporated Foundation ($16,000, 2007)  
Percentage of Effort: 20% involvement

3. Impact of Oximetry on Disposition in Acute Bronchiolitis  
Physicians Services Incorporated Foundation ($163,000, 2007-2009)  
Percentage of Effort: 10% involvement  
Annual state/federal/commercial/private support: None  
Active grants: None  
Proposals under review: None  
Proposals being prepared for submission: None

Andrew R. Willan, PhD  
Senior Scientist, Population Health Sciences  
The Hospital for Sick Children  
Professor of Department of Public Health Sciences, University of Toronto  
Start Date: 2002.07.01  
End Date: None  
Source of funding:  
Annual state/federal/commercial/private support: None  
Active grants:

1. Multiple Courses of Antenatal Corticosteroids for Preterm Birth Study: 5 Year Follow-Up
2. The Twin Birth Study  
Canadian Institute of Health Research (2003-2011 $8,608,045)  
Percentage of Effort: 5% involvement

3. Translating research on pain in children  
Canadian Institute of Health Research (2006-2011 $5,928,858)  
Percentage of Effort: 5% involvement

4. Development of statistical methodology in cost-effectiveness analysis  
Natural Sciences and Engineering Research Council of Canada (2003-2008 $44,000)  
Percentage of Effort: 70% involvement

5. Emergency Department Rapid Intravenous Rehydration for Pediatric Gastroenteritis: A Randomized Controlled Trial  
Physicians Services Incorporated Foundation (2006-2007 $156,000)  
Percentage of Effort: 5% involvement

6. Early External Cephalic Version 2-Trial  
Canadian Institute of Health Research (2003-2007 $2,853,717)  
Percentage of Effort: 5% involvement

7. SELAN (Structured Early Labour Assessment and Care)  
Canadian Institute of Health Research (2003-2007 $665,668)  
Percentage of Effort: 5% involvement

Proposals under review: None  
Proposals being prepared for submission: None

Wendy Ungar, M. Sc, PhD  
Senior Scientist, Child Health Evaluative Sciences  
The Hospital for Sick Children  
Associate Professor, Department of Health Policy, Management and Evaluation, Faculty of Medicine, University of Toronto  
Start Date: March 1999  
End Date: None  
Source of funding: CIHR, AllerGen NCE, Organization of Teratology Information Services  
Annual state/federal/commercial/private support: None  
Active grants:  
1. An economic evaluation of teratology information services (TIS)  
Organization for Teratology Information Services (2006-2008 $50,000 US)  
Percentage of Effort: 10%

2. Costs incurred by families of children newly diagnosed with cancer  
National Cancer Institute of Canada (2006-2008 $356,822)  
Percentage of Effort: 2.5%

3. The Ulysses Program: Building Research Capacity in Health Technology Assessment and Management  
Canadian Coordinating Office for Health Technology Assessment (2006-2007 $99,728)  
Percentage of Effort: 10%

4. Costs Incurred by Families of Children Newly Diagnosed with Cancer  
Paediatric Oncology Group of Ontario (2006-2008 $55,000)  
Percentage of Effort: 2.5%

5. Financial barriers to medication use in children with asthma: effect on health outcome  
AllerGen National Centre for Excellence (2005-2007 $100,000)  
Percentage of Effort: 25%

Evaluation and Decision-Making
The Canadian Institutes of Health Research (2004-2007 $224,726)
Percentage of Effort: 25%

7. The Pediatric Economic Database Evaluation (PEDE) Project
Percentage of Effort: 2%

8. Pharmaceutical cost-sharing and health outcomes in children with asthma
The Canadian Institutes of Health Research and Hospital for Sick Children Research Institute New Investigator Career Award (2002-2007 $250,000)
Percentage of Effort:

9. Fetal Alcohol Syndrome: Oxidative Stress and Innovative Therapies
Canadian Institutes of Health Research New Emerging Team (2002-2007 $1,250,000)
Percentage of Effort: 1%

Proposals under review:

1. Management proposal for CADTH’s partners in health technology assessment
Submitted to Canadian Agency for Drugs and Technologies in Health December 2006
Percentage of Effort:

2. Young infants with acute recurrent wheezing - to puff or not to puff? A randomized controlled trial
Submitted to Hospital for Sick Children Foundation October 2006
Percentage of Effort:

3. Antidepressants and Risk of Suicide or Self-harm in Canadian Youth: A national population-based study.
Submitted to The Canadian Institutes of Health Research September 2006
Percentage of Effort:

Zelia Da Silva, RT
Respiratory Technologist, Division of Respiratory Medicine
The Hospital for Sick Children
Start Date: 1993
End Date: None
Source of funding: None
Annual state/federal/commercial/private support: None
Active grants: None
Proposals under review: None
Proposals being prepared for submission: Collaborator: Efficacy of Cold Air in the Treatment of Croup
Percentage of Effort: 5%
Biographical Sketch

Do not exceed two pages per biographical sketch.

Give the following information for key personnel, beginning with the principal investigator.

Name: Suzanne Schuh

Title: Staff Pediatrician and Research Director, Emergency Department

The Hospital for Sick Children

Senior Associate Scientist, Research Institute

Professor of Pediatrics, University of Toronto

Education

Begin with baccalaureate or other initial professional education, and include all postdoctoral training.

<table>
<thead>
<tr>
<th>Institution and location</th>
<th>Degree</th>
<th>Year</th>
<th>Field of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>The University of Toronto, Toronto, Ontario</td>
<td>B.Sc.</td>
<td>1973</td>
<td>Science</td>
</tr>
<tr>
<td>The University of Toronto, Toronto, Ontario</td>
<td>M.D. (Honours)</td>
<td>1977</td>
<td>Medicine</td>
</tr>
<tr>
<td>The American Board of Pediatrics</td>
<td>FAAP</td>
<td>1981</td>
<td>Pediatrics</td>
</tr>
<tr>
<td>The University of Toronto, Toronto, Ontario</td>
<td>FRCP(C)</td>
<td>1981</td>
<td>Pediatrics</td>
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</tbody>
</table>

Research or Professional Experience

Concluding with your present position, list in chronological order all previous employment, experience, and honors. List in chronological order complete references to all publications during the past three years and to representative earlier publications pertinent to this application.

Previous Employment:

1982 - 1984 Consultant paediatric practice, Oshawa Clinic, Oshawa, Ontario

1983 - 1984 Part-time staff Emergency Department and General Paediatrics, The Hospital for Sick Children, Toronto, Ontario

1985 - Present Full-time Staff Emergency Department, The Hospital for Sick Children, Toronto, Ontario

1992 - 2000 Paediatric Emergency Fellowship Director, The Hospital for Sick Children, Toronto, Ontario

1998 - 2005 Associate Scientist, Research Institute, The Hospital for Sick Children, Toronto, Ontario

2000 - Present Emergency Research Director, The Hospital for Sick Children, Toronto, Ontario

2005 - Present Senior Associate Scientist, Research Institute, The Hospital for Sick Children, Toronto, Ontario

Honours:

Paediatric Trainee Research Award for Best Subspecialty Poster, Research Institute, The Hospital for Sick Children. Does Oximetry Predict Length of Therapy in Children with Acute Asthma? 2003

Best Research Design - University of Toronto Emergency Medicine Award. Does Oximetry predict length of therapy in children with acute asthma. 2003

University of Toronto Faculty of Medicine Physician Research Award for Career Excellence. Nominated for this award. February 2007

Publications:


To insert another biographical sketch, make sure macros are enabled, and then press the ALT and 1 keys (ALT + 1). For instructions on enabling macros, see: http://office.microsoft.com/assistance/2002/articles/pwMacroSecurity.aspx
Biographical Sketch  
Do not exceed two pages per biographical sketch.

Give the following information for key personnel, beginning with the principal investigator.

Name: Stephen Freedman

Title: Staff Pediatrician, Emergency Dept.
The Hospital for Sick Children
Assistant Professor of Pediatrics
University of Toronto

Education
Begin with baccalaureate or other initial professional education, and include all postdoctoral training.

<table>
<thead>
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<th>Institution and location</th>
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<th>Field of study</th>
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<tr>
<td>McGill University</td>
<td>Medicine Preparatory Year</td>
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<td>Pre-medicine</td>
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<tr>
<td>McGill University</td>
<td>MDCM</td>
<td>1996</td>
<td>Medicine</td>
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<tr>
<td>Northwestern University</td>
<td>MSCl</td>
<td>2003</td>
<td>Master Degree in Clinical Investigation</td>
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Research or Professional Experience
Concluding with your present position, list in chronological order all previous employment, experience, and honors. List in chronological order complete references to all publications during the past three years and to representative earlier publications pertinent to this application.

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<tr>
<th>Previous Employment:</th>
<th>2000 - 2001</th>
<th>Associate Staff, The Hospital for Sick Children, Toronto, Ontario</th>
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<tr>
<td>2002 - 2004</td>
<td>Affiliate, Division of General Medicine, Children's Memorial Hospital, Chicago, IL</td>
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<tr>
<td>2003 - 2004</td>
<td>Provisional, Division of Emergency Medicine, Northwest Community Hospital, Chicago, IL</td>
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<tr>
<td>2004</td>
<td>Associate, Division of Emergency Medicine, Northwestern Community Hospital, Chicago, IL</td>
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<tr>
<td>Oct 2004 - Present</td>
<td>Staff Physician, The Hospital for Sick Children, Toronto, Ontario</td>
<td></td>
</tr>
<tr>
<td>May 1, 2005 - Nov 13, 2006</td>
<td>Project Director, Research Institute, The Hospital for Sick Children, Toronto, Ontario</td>
<td></td>
</tr>
<tr>
<td>Nov 13, 2006 - Present</td>
<td>Associate Scientist, Child Health Evaluative Sciences Program, Research Institute, Hospital for Sick Children, Toronto, Ontario</td>
<td></td>
</tr>
</tbody>
</table>

Honours:
Division of Paediatric Emergency Medicine, Clinical Recognition Award-MD, Runner Up. In recognition of excellence in outstanding effort & contribution to the Emergency Department. 2006
Division of Paediatric Emergency Medicine, Research Recognition Award-MD. In recognition of excellence in outstanding effort & contribution to research. 2006

Publications:
Principal Investigator: Suzanne Schuh

Biographical Sketch

Do not exceed two pages per biographical sketch.

Give the following information for key personnel, beginning with the principal investigator.

Name: Allan Coates

Title: Division of Respiratory Medicine
The Hospital for Sick Children
Professor of Pediatrics
University of Toronto

Education

Begin with baccalaureate or other initial professional education, and include all postdoctoral training.

<table>
<thead>
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<th>Institution and location</th>
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<th>Year</th>
<th>Field of study</th>
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<tbody>
<tr>
<td>McGill University</td>
<td>B.Eng.(Elect.)</td>
<td>1967</td>
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</tr>
<tr>
<td>Montreal, Quebec</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McGill University</td>
<td>M.D.C.M.</td>
<td>1972</td>
<td></td>
</tr>
<tr>
<td>Montreal, Quebec</td>
<td></td>
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</tbody>
</table>

Concluding with your present position, list in chronological order all previous employment, experience, and honors. List in chronological order complete references to all publications during the past three years and to representative earlier publications pertinent to this application.

Previous Employment:

1977-1996 Full-time Member of the Respiratory Medicine Service, The Montreal Children’s Hospital

1984-1985 Acting Director, Newborn Medicine, The Montreal Children’s Hospital

1984-1996 Co-Director BPD Clinic, The Montreal Children’s Hospital

1987-1993 Director Cystic Fibrosis Clinic, The Montreal Children’s Hospital

1988-1989 Acting Director, Respiratory Medicine Service, The Montreal Children’s Hospital

1989-1996 Co-Director, McGill Respiratory Training Program

1989-1996 Director, Respiratory Medicine Service, The Montreal Children’s Hospital


1997-2005 Director, Division of Respiratory Medicine, Hospital for Sick Children

1998-2004 Associate Head in the Integrative Biology Program- Research Institute, Hospital for Sick Children

2005- Staff Physician, Division of Respiratory Medicine, Hospital for Sick Children

2006- Medical Director, Pulmonary Function Lab, Division of Respiratory Medicine, Hospital for Sick Children

Honours:

N/A

Publications:


Biographical Sketch

Do not exceed two pages per biographical sketch.

Give the following information for key personnel, beginning with the principal investigator.

Name: Patricia Parkin

Title: Division of Pediatric Medicine
The Hospital for Sick Children
Associate Professor of Pediatrics
University of Toronto

Education Begin with baccalaureate or other initial professional education, and include all postdoctoral training.

<table>
<thead>
<tr>
<th>Institution and location</th>
<th>Degree</th>
<th>Year</th>
<th>Field of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>University of Toronto, Trinity College</td>
<td>B.Sc</td>
<td>1979</td>
<td></td>
</tr>
<tr>
<td>The Medical Council of Canada</td>
<td>LMCC</td>
<td>1982</td>
<td></td>
</tr>
<tr>
<td>McMaster University Medical School</td>
<td>M.D</td>
<td>1982</td>
<td></td>
</tr>
<tr>
<td>American Academy of Pediatrics Fellow</td>
<td>F.A.A.P.</td>
<td>1987</td>
<td></td>
</tr>
<tr>
<td>Royal College of Physicians and Surgeons</td>
<td>FRCP (C)</td>
<td>1987</td>
<td>Pediatrics</td>
</tr>
<tr>
<td>of Canada</td>
<td></td>
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</tr>
</tbody>
</table>

Research or Professional Experience

Concluding with your present position, list in chronological order all previous employment, experience, and honors. List in chronological order complete references to all publications during the past three years and to representative earlier publications pertinent to this application.

Previous Employment:

1989 – Present  Active Staff Pediatrician, Division of Pediatric Medicine, The Hospital for Sick Children, Toronto, Ontario
1989 – 1997    Director, Pediatric Medicine Consult Team, Division of Pediatric Medicine, The Hospital for Sick Children, Toronto, Ontario
1990 – Present Consultant Pediatrician, Pediatric Neurofibromatosis Clinic, Division of Pediatric Medicine, The Hospital for Sick Children, Toronto, Ontario
1994 – 1997    Director, Pediatric Medicine Inpatient Unit, Division of Pediatric Medicine, The Hospital for Sick Children, Toronto, Ontario
1997 – 2000    Acting Director, Pediatric Outcomes Research Team (PORT), Division of Pediatric Medicine, The Hospital for Sick Children, Toronto, Ontario
1997 – 2004    Head, Division of Pediatric Medicine, The Hospital for Sick Children, Toronto, Ontario
2004 – Present Director, Pediatric Outcomes Research Team (PORT), The Hospital for Sick Children, Toronto, Ontario
2004 – Present Director, Research and Fellowship Program, Division of Pediatric Medicine, The Hospital for Sick Children, Toronto, Ontario

Honours:

Harry Bain Award for Excellence in Clinical Teaching, Department of Pediatrics. University of Toronto, Hospital for Sick Children. 1999

Publications:


To insert another biographical sketch, make sure macros are enabled, and then press the ALT and 1 keys (ALT + 1). For instructions on enabling macros, see: http://office.microsoft.com/assistance/2002/articles/pwMacroSecurity.aspx
Biographical Sketch

Do not exceed two pages per biographical sketch.

Give the following information for key personnel, beginning with the principal investigator.

Name: Upton Allen
Title: Director, Division of Infectious Diseases
The Hospital for Sick Children
Professor of Pediatrics
University of Toronto

Education

Begin with baccalaureate or other initial professional education, and include all postdoctoral training.

<table>
<thead>
<tr>
<th>Institution and location</th>
<th>Degree</th>
<th>Year</th>
<th>Field of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>University of The West Indies, Kingston, Jamaica</td>
<td>MBBS</td>
<td>1981</td>
<td></td>
</tr>
<tr>
<td>McMaster University, Hamilton, Ontario</td>
<td>MSc</td>
<td>1990</td>
<td>Design Measurement and Evaluation</td>
</tr>
<tr>
<td>The Hospital for Sick Children, Toronto, Ontario</td>
<td>FRCPC, FAAP</td>
<td>1987</td>
<td></td>
</tr>
</tbody>
</table>

Research or Professional Experience

Concluding with your present position, list in chronological order all previous employment, experience, and honors. List in chronological order complete references to all publications during the past three years and to representative earlier publications pertinent to this application.

Previous Employment:

1991-1995: Assistant Professor of Pediatrics, Division of Infectious Diseases, Children’s Hospital of Eastern Ontario, University of Ottawa.
Program Director, Subspecialty Training in Pediatric Infectious Diseases, Children’s Hospital of Eastern Ontario, University of Ottawa.
Director, Pediatric HIV Clinic, Children’s Hospital of Eastern Ontario
Consulting Staff (Infectious Diseases), Ottawa General Hospital

11/2003 -> current Chief, Division of Infectious Diseases, Hospital for Sick Children.
06/2005 -> current Senior Associate Scientist, Research Institute, Hospital for Sick Children.
2006 -> current Professor of Pediatrics, Division of Infectious Diseases, Department of Paediatrics, Hospital for Sick Children, University of Toronto

Honours:

2004 Appointed to Credentials Committee, Royal College of Physicians and Surgeons of Canada.
2005 Selected for Distinguished Poster Faculty session, Infectious Diseases Society of America Meeting, 2005.
2005 Promoted to Senior Associate Scientist, Research Institute, Hospital for Sick Children.
2005 Visiting Professor, Commission Training for Paediatrics, Hospital Authority, Hong Kong in Collaboration with the University of Hong Kong and the Chinese University of Hong Kong.
2006 Promoted to Full Professor, University of Toronto
2006 External Examiner, University of the West Indies, Jamaica
2006 Visiting Professor, University of Calgary

Publications:

20. Allen U. Public health implications of MRSA in Canada. Allen UD. CMAJ 2006; 175;161. PA
22. Allen U and the Infectious Diseases and Immunization Committee. Canadian Paediatric Society (CPS). Current management of herpes simplex virus infection in pregnant women and their newborn infants. Paediatr Child Health 2006;11;363-5 PA

To insert another biographical sketch, make sure macros are enabled, and then press the ALT and 1 keys (ALT + 1). For instructions on enabling macros, see: http://office.microsoft.com/assistance/2002/articles/pwMacroSecurity.aspx
Principal Investigator: Suzanne Schuh

Biographical Sketch  Do not exceed two pages per biographical sketch.

Give the following information for key personnel, beginning with the principal investigator.

Name: Andrew Willan

Title: Senior Scientist, Population Health Sciences
       The Hospital for Sick Children
       Professor of Department of Public Health Sciences
       University of Toronto

Education  Begin with baccalaureate or other initial professional education, and include all postdoctoral training.

<table>
<thead>
<tr>
<th>Institution and location</th>
<th>Degree</th>
<th>Year</th>
<th>Field of study</th>
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<tbody>
<tr>
<td>Department of Epidemiology and Biostatistics University of Western Ontario, London ON</td>
<td>PhD</td>
<td>1979</td>
<td>Biostatistics</td>
</tr>
<tr>
<td>Queen's University, Kingston ON</td>
<td>MSc</td>
<td>1976</td>
<td>Statistics</td>
</tr>
<tr>
<td>Queen's University, Kingston ON</td>
<td>Bed</td>
<td>1972</td>
<td>Mathematics and Physical Education</td>
</tr>
<tr>
<td>York University, Toronto ON</td>
<td>BA</td>
<td>1970</td>
<td>Economics and Mathematics</td>
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Research or Professional Experience

Concluding with your present position, list in chronological order all previous employment, experience, and honors. List in chronological order complete references to all publications during the past three years and to representative earlier publications pertinent to this application.

Previous Employment:

September 1981 to August 1987 - Assistant Professor, Department of Community Health and Epidemiology, Queen's University, Kingston ON.

April 1985 to August 1987 - Head of Biometry with the Clinical Trials Group, National Cancer Institute of Canada, Queen's University, Kingston ON.

September 1987 to February 1989 - Associate Professor, Department of Population Medicine, University of Guelph, Guelph ON

March 1989 to October 1991 - Associate Professor, Department of Preventive Medicine and Biostatistics, University of Toronto, Toronto ON

January 1989 to May 1990 - Head, Division of Clinical Trials and Epidemiology, Sunnybrook Health Science Centre, Toronto ON

September 1990 to June 1993 - Associate Professor, Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton ON

September 1993 to June 2002 - Professor, Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton ON

Senior Scientist, Population Health Sciences, SickKids Research Institute, Toronto Professor, Population Health Sciences, University of Toronto Professor Emeritus, Clinic Epidemiology and Biostatistics, McMaster University

Honours:

Co-author on a paper receiving the International Society for Pharmaco-economics and Outcomes Research Award for Methodology Excellence, awarded May 2003.

Co-author on a paper receiving the International Society for Pharmaco-economics and Outcomes Research Award for Methodology Excellence, awarded May 2002.

Publications:


19. Willan AR. Clinical decision making and the expected value of information. *Clinical Trials* (accepted for publication). 


Principal Investigator: Suzanne Schuh
Biographical Sketch

Do not exceed two pages per biographical sketch.

Give the following information for key personnel, beginning with the principal investigator.

Name: Wendy Ungar

Title: Senior Scientist, Population Health Sciences
Associate Professor, Department of Health Policy, Management and Evaluation, Faculty of Medicine, University of Toronto
Adjunct Scientist, Institute for Clinical Evaluative Sciences

Education

Begin with baccalaureate or other initial professional education, and include all postdoctoral training.

<table>
<thead>
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<th>Institution and location</th>
<th>Degree</th>
<th>Year</th>
<th>Field of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>University of Toronto, Ontario, Canada</td>
<td>Ph.D.</td>
<td>1997</td>
<td>Faculty of Medicine</td>
</tr>
<tr>
<td>McGill University, Montreal, Quebec, Canada</td>
<td>M.Sc.</td>
<td>1984</td>
<td>Pharmacology and Therapeutics</td>
</tr>
<tr>
<td>Brandeis University, Boston, Massachusetts, U.S.A.</td>
<td>B.A.</td>
<td>1981</td>
<td>Biology</td>
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</table>

Research or Professional Experience

Concluding with your present position, list in chronological order all previous employment, experience, and honors. List in chronological order complete references to all publications during the past three years and to representative earlier publications pertinent to this application.

Previous Employment:

1985-1987 Research Associate, Pharmaceutical Clinical Research, Bristol-Myers Pharmaceutical Group, Ottawa, Ontario
1987-1990 Manager, Pharmaceutical Clinical Research, Bristol-Myers Pharmaceutical Group, Ottawa, Ontario
1991-1993 Associate Director/Clinical Project Manager, Ciba-Geigy Canada Ltd., Mississauga, Ontario
1996-1997 Health Economics and Health Services Research Consultant
1999-2005 Associate Member, Faculty of Graduate Studies, University of Toronto
1999-2006 Assistant Professor, Department of Health Policy, Management and Evaluation, University of Toronto
1999-2006 Scientist, Population Health Sciences, Hospital for Sick Children
2005-present University of Toronto Program Director, International Masters Degree in Health Technology Assessment & Management (Ulysses Program)
2006-present Associate Professor, Department of Health Policy, Management and Evaluation, University of Toronto

Honours:

2002-2007 New Investigator Award, Canadian Institutes of Health Research
2005 Canadian Health Services Research Foundation CAN! Award
2006 Canadian Health Services Research Foundation CAN! Award

Publications:

To insert another biographical sketch, make sure macros are enabled, and then press the ALT and 1 keys (ALT + 1). For instructions on enabling macros, see: http://office.microsoft.com/assistance/2002/articles/wMacroSecurity.aspx
Biographical Sketch

Do not exceed two pages per biographical sketch.

Give the following information for key personnel, beginning with the principal investigator.

Name: Zelia Da Silva
Title: Registered Respiratory Therapist
Department of Respiratory Therapy
The Hospital for Sick Children

Education

Begin with baccalaureate or other initial professional education, and include all postdoctoral training.

<table>
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<tr>
<th>Institution and location</th>
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<tr>
<td>The Michener Institute for Applied Health Sciences</td>
<td>Respiratory Therapy Program</td>
<td>1993</td>
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<tr>
<td>Toronto, Ontario</td>
<td></td>
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<tr>
<td>Critical Care Unit</td>
<td>Clinical Teaching Techniques Certificate Course</td>
<td>1997</td>
<td></td>
</tr>
<tr>
<td>The Hospital for Sick Children</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Master of Applied Science (Respiratory Science)</td>
<td>Collaborative Michener/Charles Sturt University Degree Completion Program</td>
<td>2004-</td>
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</table>

Research or Professional Experience

Concluding with your present position, list in chronological order all previous employment, experience, and honors. List in chronological order complete references to all publications during the past three years and to representative earlier publications pertinent to this application.

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<tr>
<td>August 1993 – February 1997</td>
<td>Staff Therapist, CCU, NICU, Acute Care (Wards/ER)</td>
<td>The Hospital For Sick Children</td>
<td></td>
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<tr>
<td>July 2003 – July 2004</td>
<td>Acting -Clinician Educator, Respiratory Therapy- MLOA</td>
<td>The Hospital For Sick Children</td>
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<tr>
<td>February 1997 – April 2005</td>
<td>Clinical Coordinator, Respiratory Therapy / Michener Institute</td>
<td>The Hospital For Sick Children</td>
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<tr>
<td>April 2005 – Present</td>
<td>Profession Leader, Respiratory Therapy</td>
<td>The Hospital For Sick Children</td>
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Honours:

The Michener Institute for Applied Health Sciences
Recipient of the 1993 Student Achievement Award

Publications:

“Efficacy of Optimal Versus Traditional Delivery of Humidity in Children with Croup”
**Principal Investigator:** Suzanne Schuh  
**Project Name:** Impact of Oximetry on Disposition in Acute Bronchiolitis

### Reviewer Information

*Please provide the names of four persons who have the expertise and competency to review your proposed project. State your present or past relationship with them, if any. When recommending reviewers, avoid any basis for potential conflict of interest or concern regarding peer reviewer objectivity.*

<table>
<thead>
<tr>
<th>Name</th>
<th>Degree</th>
<th>Title</th>
<th>Address</th>
<th>City</th>
<th>State</th>
<th>Zip code</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Dr. David Johnson</td>
<td>MD</td>
<td>Associate Professor of Pediatrics, University of Calgary, Alberta Children’s Hospital</td>
<td>1820 Richmond Road S.W.</td>
<td>Calgary</td>
<td>AB</td>
<td>T2T 5C7</td>
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<tr>
<td><strong>Telephone</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>403-943-7507</td>
<td>Fax</td>
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</tr>
<tr>
<td>403-943-7649</td>
<td>Email</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>2. Dr. Joseph Zorc</td>
<td>MD</td>
<td>Emergency Physician and Investigator, The Children’s Hospital of Philadelphia</td>
<td>34th and Civic Center Blvd.</td>
<td>Philadelphia</td>
<td>PA</td>
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**Relationship to investigator:** None