A SURVEY OF CANADIAN MEDICAL STUDENT ATTITUDES TOWARDS THE ETHICS OF PEDIATRIC CLINICAL TRIALS: ARE THEY DIFFERENT FROM CANADIAN AND BRITISH HEALTH CARE PROFESSIONALS?

Dianna Wang*[1,2], Allison L Bahm*[1,3], Jamie A Seabrook[4,5], Helen M Sammons[6], Michael J Rieder[7]

*Co first-authors; [1]Schulich School of Medicine and Dentistry, University of Western Ontario, London, Ontario, Canada; [2]Children's Hospital of Eastern Ontario, Ottawa, Ontario; [3]The Hospital for Sick Children, Toronto, Ontario; [4]Departments of Paediatrics and Sociology, University of Western Ontario, London, Ontario, Canada; [5]Children's Health Research Institute, Children's Hospital of Western Ontario, London, Ontario, Canada; [6]Academic Division of Child Health, University of Nottingham, Medical School, Derbyshire Children's Hospital, Uttoxeter Road, Derby, DE22 3DT, UK; [7]Section of Paediatric Clinical Pharmacology, Children's Hospital of Western Ontario, London, Ontario, Canada

Corresponding Author: abahm2009@meds.uwo.ca

ABSTRACT

Background
Due to ethical concerns and constraints inherent to research in children, the conduct of clinical trials in children has often been difficult. The views of medical professionals and trainees towards conducting clinical trials in children have been largely unexplored and are potentially important towards working to increase the number of appropriate trials conducted in children.

Objective
To explore the views of Canadian medical school trainees towards paediatric clinical trials and to compare these views with that of an earlier pilot study conducted amongst Canadian and British health care professionals.

Methods
Participants were given a questionnaire which consisted of direct questions as well as scenarios with ethical dilemmas. Responders were asked to state whether they would enter children in the trial documented in the scenario and to justify their reasons.

Results
89 questionnaires were collected (74% response rate). 42% had formal teaching regarding paediatric ethical dilemmas but only 2% had formal teaching on pharmaceutical testing in children. The students were divided on whether children should only participate in trials where they receive direct benefit. Most students (85%; 95% CI: 77% to 91%) were comfortable with non-inferiority trials even with post-hoc consent. Only a third (33%; 95% CI: 24% to 43%) agreed with the use of placebo in an analgesia trial.

Conclusion
Teaching on the ethics of paediatric clinical trials still appears to be lacking amongst medical trainees. However, there does seem to be increased willingness on the part of trainees compared to practicing medical professionals in enrolling children in clinical trials.

Key Words: *Questionnaire; ethics; child; clinical trials*

Off-label and unlicensed drug prescribing is a common practice in paediatric care, with over half of prescriptions falling under these categories.[1] Only 20-30% of drugs approved by the US Food and Drug Administration (FDA) are labelled for paediatric use[2], and extrapolating information from adult studies and generalizing to children can be dangerous as biological response to disease changes through childhood.[3] Therefore, most experts believe medications need to be tested in children before widespread use. The FDA, for example, through legislation has encouraged paediatric clinical trials by providing incentives to pharmaceutical companies that include children in studies, and by requiring paediatric randomized controlled trials before approving drugs in children.[2] In addition, several organizations, such as the American Academy of Pediatrics (AAP), National Institute of Health (NIH) and Medical Research Council (MRC), have issued position statements that detail the importance of randomized controlled trials in children.[4] Despite this consensus, there is reluctance among study investigators to include children in studies, citing reasons such as possible adverse effects, invasive procedures, ethical concerns, or anticipated patient refusal.[5] Ethical review boards appear to have no conceptual framework or criteria for judging the risks versus benefits of paediatric clinical trials[4] and are often reluctant to approve non-therapeutic protocols in children.

A recent study by Sammons et al. in 2007[6] noted that there is little research on the changing views of paediatricians and researchers in this controversial area. Their study administered questionnaires with trial scenarios containing ethical dilemmas to people involved in paediatric clinical trials in Britain and Canada. The purpose of our current study was to assess the ethical views of medical students on the use of children in clinical trials. To date, there is a paucity of research on this topic, with there being no studies assessing this issue among medical students.

METHODS

Study Population

The study was carried out among third year medical students at the University of Western Ontario (UWO) in 2008. Students were near the end of their clerkship year and had either completed or were in the process of completing their paediatrics rotation. The authors did not complete the survey to minimize bias. A convenience sample approach was used with the goal of obtaining 100 surveys. Surveys were distributed in August at a mandatory class for the students and continued to be distributed on an ongoing basis to those who were not in attendance to maximize response rate. Ultimately, a total of 121 surveys were distributed. The questionnaire was approved by the UWO Research Ethics Board.

Questionnaire

The questionnaire was similar to that used previously by Sammons et al.[6] The questionnaire consisted of three proposed clinical scenarios followed by both open and closed ended questions (*see Appendix 1*). Questions were also asked to elicit information regarding participant demographics as well as ethics training they have received in the past. Respondents were also asked to give their agreement or disagreement on a Likert scale with regards to direct questions on certain ethical issues in paediatric research. They were also asked for their opinion on the minimum age for consent and assent in paediatric research. There were no identifying factors collected in the questionnaire.

Clinical Scenarios

Three clinical scenarios were utilized, each dealing with a different ethical dilemma. The first scenario involves the use of healthy children in research to investigate the pharmacokinetics of an antibiotic for use in children with cystic fibrosis, something that would normally occur in adults. The second involves the comparison of two established anti-seizure medications with consent being obtained after randomization and treatment. The third scenario involves the comparison of an analgesic (which has proven efficacy and safety in adults) to a placebo. Respondents were asked if they would feel comfortable entering children into the trial and to justify their response in a subsequent open-ended question.

Data Analysis

The data were entered into SPSS, version 16.0. The data were then compared to results obtained in a pilot study carried out on UK and Canadian health care workers in 2005. The median and interquartile range was used to summarize continuous variables. Categorical outcome variables were reported as percentages with 95% confidence intervals (CI).

RESULTS

Demographics

Of the 121 surveys distributed, 89 were completed giving a response rate of 74%. Of the respondents, 48% were female and 45% male (7% did not report sex). Approximately half (54%) of the participants were 25 years of age or younger, 36% were 26-29 years old, and 5% were 30-35 years old (5% did not report age). Students reported that 71% received his/her initial ethics training through the UWO medical curriculum, 26% received it through an undergraduate course, and 3% received it by other means. In terms of formal teaching, 82% reported having formal teaching in adult ethical dilemmas, 42% had formal teaching in paediatric ethical dilemmas, and 40% had formal exam questions on ethical dilemmas. This teaching was in the format of lectures (90%), case studies (75%), seminars (58%) and bedside teaching (34%). When respondents were asked if they received any formal teaching on the problems of testing medicines in children, only 2% answered yes.

Direct Questions

Responses to the ethical questions associated with clinical research studies in children are reported in Table 1. Interestingly, 66% (95% CI: 56% to 76%) of Canadian medical students believed that children may be physically harmed by participation in clinical trials, compared to 88% (95% CI: 75% to 94%) of UK health professionals. Almost half (44%) of the medical students agreed that it is ethical to conduct drug trials in healthy children, while approximately half (49%) felt that children should only participate in trials in which they receive direct benefit. Forty-five percent (95% CI: 35% to 55%) of medical students also agreed that financial payment should be provided to families for compensation in the study, and 25% (95% CI: 17% to 35%) of medical students agreed with magazine advertising for recruitment of paediatric research subjects. The median age that medical students felt a child could be capable of consent to trials was 16 years (IQR=2, range=8-18) and assent was 12 years (IQR=6, range=2-18).

Clinical Trial Scenarios

Responses to the clinical trial scenarios for Canadian medical students, Canadian medical professionals and UK medical professionals are displayed in Table 2.

Scenario 1: A pharmacokinetic dose finding study in healthy children of a new antibiotic for use in cystic fibrosis. Approximately half (49%; 95% CI: 39% to 60%) of the Canadian medical students would consider entering children into this trial, compared to 45% (95% CI: 32% to 59%) of Canadian Health Professionals and only 23% (95% CI: 13% to 37%) of UK health professionals. Of the participants who disagreed or were unsure, the top issues with trial design were concerns over: drug safety (40%) and using healthy children (33%).

Scenario 2: A study comparing two emergency treatments for seizures (both drugs already in current use within paediatrics) with post-hoc consent being sought from parents after treatment for use of their child's data. Eighty-five percent of Canadian medical students (95% CI: 77% to 91%) would enter children into this trial. Of the responders who disagreed or were unsure, the main ethical concern identified was post-hoc consent (46%), and 15% had concerns over drug delivery (preference of oral drug over rectal administration).

Scenario 3: A trial of a new analgesic agent being compared to the current treatment and placebo following tonsillectomy. Only a third (33%; 95% CI: 24% to 43%) of Canadian medical students would enter children into this clinical trial. among those who disagreed or were unsure, the main concern with this trial design was use of placebo for pain control (68%). Issues with the drug safety/efficacy were also mentioned (15%).

TABLE 1 Direct questions relating to ethical dilemmas in paediatric clinical trials

Question	Response	Canadian Medical Students n (%; 95% C.I.)[a]	Canadian Health Professionals n (%; 95% C.I.)[a]	UK Health Professionals n (%; 95% C.I.)[a]
Drugs used for a general paediatric condition (e.g. asthma) may benefit all children - therefore research can be carried out in healthy children.	Agree	38 (44%; 34% to 55%)	13 (32%; 20% to 47%)	14 (30%; 19% to 45%)
Children should only participate in trials from which they receive a direct benefit.	Agree	42 (49%; 39% to 59%)	24 (59%; 43% to 72%)	23 (47%; 34% to 61%)
Healthy children may be physically harmed from participation in clinical trials.	Agree	55 (66%; 56% to 76%)	32 (80%; 65% to 89%)	42 (88%; 75% to 94%)
Advertisement in a teenage magazine could be used to recruit healthy teenagers into a clinical trial.	Agree	22 (25%; 17% to 35%)	13 (33%; 21% to 49%)	11 (22%; 13% to 35%)
Financial payment should be given to children and their families to compensate for their time taken in participating in a study.	Agree	39 (45%; (35% to 55%)	16 (39%; (26% to 54%)	20 (42%; (29% to 56%)
Age of consent (median)		16 (IQR 2)	15 (IQR 4)	14 (IQR 4)
Age of assent (median)		12 (IQR 6)	9 (IQR 5)	10 (IQR 4)

IQR Interquartile range; [a]Percentage of those who responded to the question

TABLE 2 Responses from three scenarios to the following question: Would you feel comfortable entering children into this trial?

Scenario	Would enter children n (%; 95% C.I.)		
	Canadian Medical Students	Canadian Health Professionals	UK Health Professionals
#1 Antibiotic for cystic fibrosis, pharmacokinetics study in healthy child	44 (49%; 39% to 60%)	22 (45%; 32% to 59%)	11 (23%; 13% to 37%)
#2 Emergency seizure treatment (buccal vs. rectal), post-hoc consent	76 (85%; 77% to 91%)	32 (67%; 52% to 78%)	48 (96%; 87% to 99%)
#3 Analgesic versus placebo in tonsillectomy	29 (33%; 24% to 43%)	21 (42%; 29% to 56%)	12 (26%; 16% to 40%)

DISCUSSION

The conduct of paediatric pharmaceutical trials has often been rife with ethical controversies. Despite this, there has been little published research on the opinions of medical staff on the ethics of research in children. In 2007, Sammons et al[6] compared British and Canadian views on the ethics of paediatrics clinical trials and found some interesting differences between the two groups of health care professionals. Our study utilized a similar questionnaire with the same clinical scenarios to elicit the views of Canadian medical students on conducting research in children. It is important to note that the scenarios we used were intended to bring out ethical issues and it was not always the correct answer to say that you would enter children into the study. In recent years, there has been an increasing demand for quality paediatric research and new initiatives aimed at decreasing off-label prescription habits.[4] It is therefore important to know the views of future health care professionals and the training that they are receiving in this field.

Scenario 1 dealt with the issue of recruiting healthy children for clinical trials and the concept of "direct benefit". In Canada, a healthy child can participate in trials with parental consent and ethics research board (ERB) approval where ERB approval is contingent on the trial as posing no greater than minimal risk to the child and the definition of minimal risk is left to the discretion of the ERB.[7] In Europe, the clinical trial directive states that children may only participate if they can gain a direct benefit from the trial.[7] In this scenario regarding testing the pharmacokinetics of an antibiotic in a healthy cohort of children, around half of the students surveyed said they would enter children into this trial, compared to less than one quarter of UK health professionals. The difference between UK professionals and Canadian students may be due to health professionals believing the study should have been carried out in the population in which the treatment was intended; in this case, children with CF.

Scenario 2 is an example of an equivalence or non-inferiority type trial. In this scenario, the primary issue identified by the participants became that of post-hoc consent. Despite this, Canadian medical students were more likely than Canadian health care professionals to enter children in this trial. At the time of the pilot study, the trial in scenario 2 was being conducted in the UK[4] and it was hypothesized that this was responsible for the larger proportion of responders in the UK who said they would enter children into this trial. However, such is not the case for the medical students, and this may indicate a shift in the views of medical trainees towards post-hoc consent and its importance as a tool to add recruitment in the emergency situation.

The use of placebo is another source of ethical controversy in the conduction of paediatric clinical trials. This issue was explored in scenario 3. In this case, only a third of the participants in the survey would enrol children in such a trial involving placebo. Oftentimes in paediatric trials (and adults as well), comparison with an established treatment should be used when available and avoid the use of a placebo. Recent guidelines by the European Commission state that a placebo should not be used when it means withholding effective treatment; however, a placebo may be considered when evidence for a particular treatment is lacking.[8]

One area where Canadian medical students differed from both the UK and Canadian professionals occurred in the direct questions, where less Canadian medical students felt that healthy children may be physically harmed from participation in clinical trials. Once again, this could possibly be related to a change in medical student attitudes towards paediatric research as Canadian medical students were more likely, or just as likely, as the one or both groups of medical professionals to enrol children in the trials outlined in the scenarios. On the other hand, this could be secondary to a lack of familiarity with paediatric research and the ethics involved amongst the medical students with just 2% of students having reported formal teaching regarding the ethics of testing pharmaceuticals in children. Children can be harmed in trials by adverse drug reactions (ADRs), but it is important we balance this against the risk of an ADR going undetected if the drug is not formally studied.

The differences in ethics training and experience between the students and the medical professionals could certainly be one explanation for the study results. It would be interesting in future research to compare the data obtained from the Canadian medical students with British medical trainees to see if there are any differences between the two groups at a similar level of training. The sample of students was also taken from only one medical school and most of the students answered that their initial ethical teaching was from the medical curriculum, which may bias the results towards what is taught by the curriculum. In addition, the students were all in their third year of school and thus the study may not have picked up differences amongst the students at different levels of training. The response rate was 74%, which means a number of students did not complete the questionnaire. This also could have biased the results. Future research could involve multi-centered questionnaires to ascertain if there is a general trend amongst Canadian trainees to be more lenient towards conducting paediatric clinical trials.

The survey could also be conducted across all years of medical school to further delineate the impact that the medical school curriculum may have on students' attitudes. Thus, there does appear to be progress in increasing the willingness of future physicians to enter children into clinical trials. However, more work will be necessary for future physicians to become more knowledgeable on the ethical issues encountered in paediatric research studies and to make informed decisions on the enrolment of children into trials.

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APPENDIX 1 - CLINICAL SCENARIOS

TRIAL 1

A new antibiotic is developed and could be used for treating children with antibiotic resistance in Cystic Fibrosis. It has had clinical trials carried out in the adult population that have shown good treatment and safety profiles. The pharmaceutical company would like to obtain a license in children and would like to carry out a pharmacokinetic dose finding study (this would normally occur in healthy adults). They propose a study on ten healthy 6-12 year old children who will receive a fourteen-day course of the antibiotic with a 2 mls blood sample taken on day 7 and 14 to check antibiotic levels in the blood.

TRIAL 2

A trial is proposed to study the emergency treatment of seizures in children comparing the treatments of Rectal Diazepam and Buccal Midazolam. Both treatments are currently in use and are accepted practice within paediatrics. Two hundred children admitted to the Emergency Department having a generalised tonic/clonic seizure would be pre-randomised to one of the two treatments. Following the treatment of the child, the parents will then be approached for consent of their child's data. Outcome will be time for seizure to stop following treatment.

TRIAL 3

Studies in adults suggest that a new analgesic agent may be of use in mild to moderate pain in children. It has a good safety profile and no major side effects have been noted. A trial is proposed to assess this medication in a double blind randomised controlled trial in one hundred and twenty children aged 6-12 years who have undergone tonsillectomy. The new analgesic will be compared to a paracetamol (acetaminophen) group and a placebo group. In the immediate post operative period, pain will be assessed by a nurse and in the 7 days post discharge period by parental pain diaries.