Parents' and children's comprehension and decision in a paediatric early phase oncology trial: a prospective study

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ABSTRACT

Objective To analyse parents' and children's understanding of consent information and assess their decision-making process in paediatric oncology.

Design Prospective observational study.

Settings Eleven French paediatric oncology units.

Patients Parents and children who have been asked to give consent for participation in an early phase trial.

Interventions Thirty-seven children and 119 parents were questioned using an audio-recorded semistructured interview.

Main outcome measures The participants' understanding of nine elements of the informed consent was assessed by comparing their answers with the informed consent leaflet. Their decision-making process was also evaluated.

Results Most parents and children had an excellent understanding regarding their participation in a clinical trial (respectively 88.2% and 48.6%), the right to withdraw (76.5% and 43.2%) and the prospects of collective benefits (74.8% and 48.6%). By contrast, less than half of the parents and few of the children correctly understood the alternatives (respectively 47.5% and 27%), the risks related to participation (44.5% and 10.8%), the prospects of individual benefits (33.6% and 10.8%) and the purpose of the clinical trial (12.6% and 2.7%). Twenty-six (70.3%) children participated in the decision-making process. Most parents and children felt they had no choice but to participate in the trial to have access to a new anticancer treatment.

Conclusions What might appear to be a poor understanding of the research protocol may actually correspond to the families' interpretation of the situation as a coping mechanism. All children (except infants) should get age-tailored information in order for them to have a meaningful involvement in research.

What is already known on this topic?

- Parents do not adequately understand all elements of a trial (eg, purpose of the trial, risks, and so on).
- Children may participate in an oncology trial unknowingly due to a lack of information.

What this study adds?

- Most parents and children understood very well the general aspects of the trial.
- Parents and children had more difficulties in understanding the specific information (eg, risks, individual benefits).
- More than half of the children participated in the decision, which showed the importance of their role in this process.

INTRODUCTION

In paediatric oncology, patients who have no remaining curative options are potential candidates for phase I or II trial, which allow access to new anticancer treatments and to investigate their toxicity (by determining the maximum tolerated dose) and preliminary efficacy.

Furthermore, although early phase trials have offered a small likelihood of benefit for the individual patients to date (average response from 5% to 10%), they may be effective in relieving or delaying the symptoms of the disease.[1] In rare cases, total remission has even been observed in certain early phase trials.[2] Parents and children must receive appropriate information regarding the risks and uncertain benefits related to participation in order for them to make an informed and autonomous decision.[3 4]

However, in the context of phase III oncology trials, parents or patients seemingly failed to adequately understand some elements of a given trial (eg, purpose of the trial, risks, and so on).[5–7] A paediatric study also found the same results with early phase oncology trials, in which only 32% of the parents understood the purpose of the research.[8]

The European regulation regarding clinical trials on medicinal products for human use established that children may take part in the informed consent (IC) process, according to their age and maturity.[9] Despite their theoretically key role, children may in fact participate in an oncology trial unknowingly.[10] To date, there have been only few studies on the understanding of IC taking into account the children's perspective.

In light of the above, the primary aim of this study was to evaluate parents' and children's understanding of consent information. The secondary aim was to analyse the decision-making process, especially in children.

MATERIAL AND METHODS

Participants

This prospective observational study was conducted in 11 French paediatric oncology units. Eligible families were parents and/or children (under 18 years old) who had been asked to give consent for participation in an early phase trial, regardless of whether they ultimately decided to participate or not. The characteristics of the trials are described in online supplementary table 1. Non-inclusion criteria were: patient's withdrawal from the early phase trial, death of the patient, parent's refusal, or a time interval exceeding 1 month since inclusion in the early phase trial.

Material

Parents and children were contacted by a psychologist to organise an audio-recorded semistructured interview. Interviews took place ideally within 1 month after they had decided to participate (or not) in an early phase trial. The participants were seen at the time of a consultation or hospitalisation to minimise additional constraints. Children participated in the study after inclusion by their physicians and parental agreement. Parents and children were met separately or together, depending on their personal preferences. Physicians answered a questionnaire regarding the child's medical data. Both interview and questionnaire frameworks were elaborated and validated by psychologists, physicians and a parent representing a patient's association.[5 6 11]

Table 1 Framework used for the interview to assess the parents' and child's understanding of the consent information

Concept	Questions asked to the parents	Questions asked to the children
Research participation	Is your child's current treatment part of a research protocol?	Is your current treatment part of a research protocol?
Purpose of the trial	What is the purpose of the trial?	What is the purpose of the trial?
Design of the trial	What is planned for your child during the course of this trial?	What is planned during the course of this trial?
Duration of participation	How long is your child expected to participate in this trial?	How long are you expected to participate in this trial?
Individual benefits	How do you think this trial will benefit your child?	How do you think this trial will benefit you?
Collective benefits	Do you think your child's participation in this trial will benefit other children?	Do you think your participation in this trial will benefit other children?
Right to withdraw	Once the trial has started, can you change your mind and decide to drop out?	Once the trial has started, can you change your mind and decide to drop out?
Risks	What are the possible risks facing your child by participating in this trial?	What are the possible risks of participating in this trial?
Alternative options	If you had not agreed to participate in this trial, what alternative care would have been provided to your child?	If you had not agreed to participate in this trial, what alternative care would have been provided to you?

Consent comprehension was assessed based on nine elements excerpted from the information leaflets given to the families in the various trials (table 1).

For both parents and children, the assessed predictive factors of a good understanding were: whether the information leaflet had been read or not, time since diagnosis (<6 months, 6 months to 2 years, >2 years), disease recurrence and previous participation to a clinical trial. Specific factors for the parents were: socioprofessional category, native French speaker, personal efforts to find additional information and time dedicated by the physicians for delivering information. Specific factors for the children were: age, sex, school grade and behaviour during the interview (subjective judgement according to the psychologist).

For both parents and children, two open questions were used to explore the reasons for their decision: 'How did you experience having to make a decision?' and 'What were the principal elements underlying your decision?' Participants could give several answers. All of the responses were taken into account and similar answers were gathered. Regarding the children's participation, children were asked regarding their participation in the final decision: 'Were you involved in the final decision, and what does it mean to you?'

Questionnaires and interviews were analysed in double-blinded manner with a validated code framework by two psychologists. The principal investigator settled any unresolved discrepancy.

Statistical analysis

Inclusion of 100 families was necessary to estimate observed proportions (50% worst-case scenario) with a prespecified precision of ±10% (alpha risk of 5%).

Comprehension for each element was graded 'excellent', 'fair' or 'poor': 'excellent' if the parents were able to fully report the specific information from the leaflet; 'fair' if they understood the element, but only partially described the latter; 'poor' if none of the information in the leaflet was mentioned. To test the influence of covariates on the comprehension of each element, both 'excellent' and 'fair' understandings were pooled and compared with 'poor' understanding.

Agreement among the different raters was assessed with a Cohen's kappa reliability test (k).

Results are expressed as numbers and percentages, or medians and IQRs when appropriate. Fisher's exact tests were carried out to compare qualitative values while Mann-Whitney tests were used to compare quantitative values. All variables with a p value <0.2 were selected for inclusion in a multivariate logistic regression analysis using a mixed effects model with a random effect for each pair of parents. The influence of covariates on the quality of understanding was also evaluated. To assess the agreement between parents' and child's responses, a mixed effects model was used considering the family as a random effect in order to account for any correlations in the responses within family members. P values <0.05 were considered to be statistically significant. Statistical analyses were performed with ad hoc routines implemented in R software (http://www.R-project.org).

RESULTS

Participants

The present study was carried out between February 2008 and June 2011, in which interviews of 119 parents (including 87 lone parents and 16 pairs) and 37 children (figure 1) were analysed. The characteristics of the parents and children participating in the study are described in online supplementary table

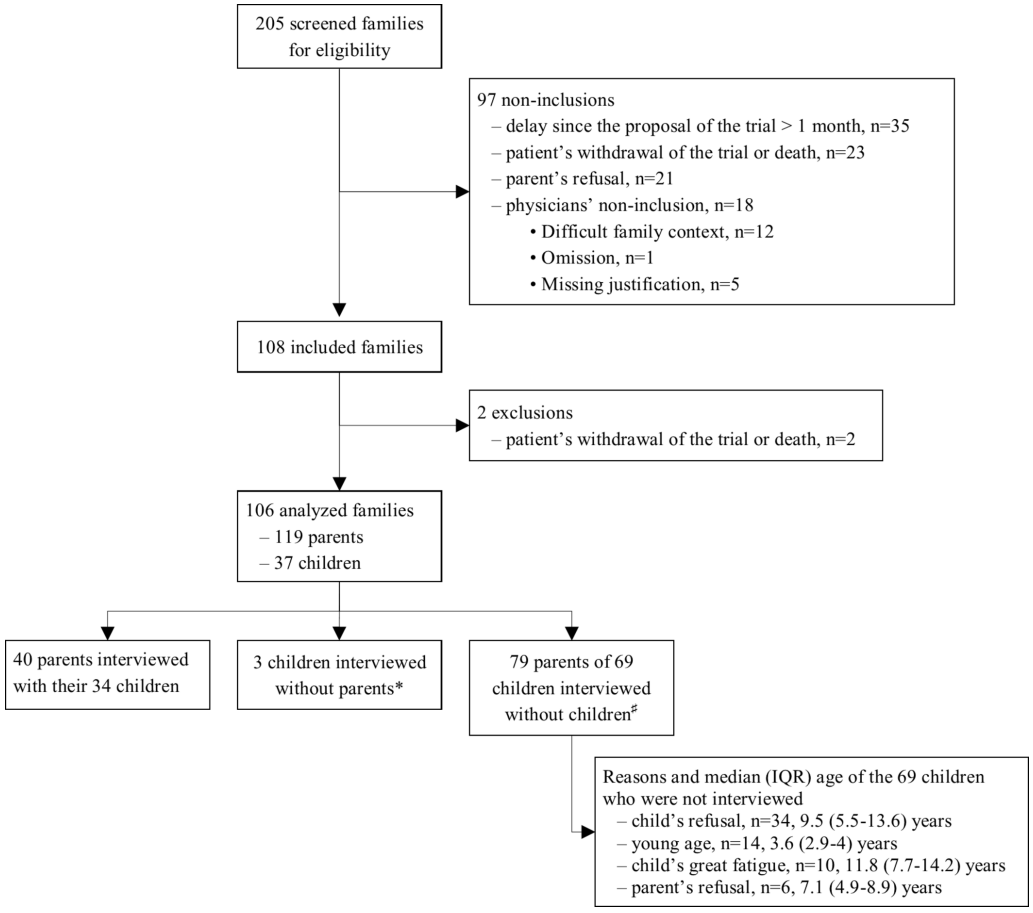

Figure 1 Trial profile. *Three children were enrolled without parents, considering family dynamics. #Only one parent who participated in our study refused to enrol her child in an early phase trial because she did not want her son to be 'considered like a guinea pig'.

2 and table 2, respectively. Ninety-three (87.7%) physicians completed the questionnaire relative to the child's medical data.

Interviews were conducted with a median (IQR) delay of 32.5 (28–42) days from the inclusion in the trial. According to the subjective judgement of the psychologists, 19 (51.4%) children participated well during the interview and 18 (48.6%) were self-contained.

All of the parents received an information leaflet. All children but six received an information leaflet appropriate for their age, despite its availability.

Coding agreement between the two psychologists was very good (k=0.81 (95% CI 0.79 to 0.83) for the parents and 0.86 (95% CI 0.83 to 0.89) for the children).

Oral information regarding the early phase trial from the perspectives of the physicians, parents and children

According to the physicians, all of the parents received information with a median (IQR) duration of information of 60 (45–70) min. Children were present during 54 (52.4%) parent-physician meetings.

Physicians, parents and children had different perspectives relative to the delivery of information to the child (table 3). According to the physicians and children, the physician had the leading role. According to the parents, the latter informed their child together with the physician in the form of teamwork.

Quality of the understanding of the IC

Figure 2 summarises the quality of the understanding based on nine elements of the IC.

The understanding by the parents of the purpose of the trial and of the potential individual benefits was poor, since their answers were the hope of a cure, in respectively 55 (46.2%) and 52 (43.7%) parents. Regarding the risks, only 53 (44.5%) parents mentioned the specific risks of the trial and 15 (12.6%) parents mentioned the vital risk. Forty-two (35.3%) parents considered the trial as the unique option. Five (4.2%) parents mentioned palliative care alone as an option.

Children understood less than their parents ($p<0.0001$). Cure was mentioned by 15 (40.5%) children as the purpose of the trial, and by 14 (37.8%) children as a prospect of individual benefit. Four (10.8%) children mentioned the specific risks of the trial. One child did not mention the vital risk or palliative care.

In multivariate analysis, consent understanding was associated with a longer time interval since diagnosis, namely over 2 years for the purpose of the trial (OR=7.52, 95% CI 1.09 to 51.99, p=0.041) and over 6 months for individual benefits (OR=7.91, 95% CI 1.2 to 51.96, p=0.031). Alternatives were best understood if the time dedicated to information was longer (OR=1.03, 95% CI 1.01 to 1.05, p=0.014).

For the children, in univariate analysis, three covariates improved the understanding of the right to withdraw: being older (15 (13.25–17) years old vs 12 (11.25–13.5) years old, p=0.02), showing interactive behaviour during the interview

Table 2 Characteristics of the children included in the early phase oncology trial and in the present study

	Participating in the early phase trial (n=106)	Participating in the present study (n=37)
Age in years, median (IQR)*	10.5 (5.6–14.1)	13.2 (11.1–15.1)
Sex ratio M/F	61/45	19/18
Out-of-school children (%)	37 (34.9)	9 (24.3)
Tumour type		
Solid tumour (%)	93 (87.7)	35 (94.6)
Neuroblastoma (%)	11 (10.4)	0
Medulloblastoma (%)	17 (16)	7 (18.9)
Rhabdomyosarcoma (%)	16 (15.1)	5 (13.5)
Ewing's sarcoma (%)	13 (12.3)	9 (24.3)
Osteosarcoma (%)	10 (9.4)	6 (16.2)
Glioma (%)	8 (7.5)	2 (5.4)
Other (%)	18 (17)	6 (16.2)
Haematologic neoplasm (%)	13 (12.3)	2 (5.4)
Acute lymphocytic leukaemia (%)	9 (8.5)	2 (5.4)
Other (%)	4 (3.8)	0
Time since diagnosis		
<6 months (%)	20 (18.9)	5 (13.5)
6 months to 2 years (%)	33 (31.1)	8 (21.6)
>2 years (%)	47 (44.3)	22 (59.5)
Missing data (%)	6 (5.7)	2 (5.4)
Recurrence of the disease (%)	66 (62.3)	26 (70.3)
Previous participation to a clinical trial (%)	33 (31.1)	6 (16.2)
Previous treatments		
Surgery (%)	62 (58.5)	23 (62.2)
Radiation therapy (%)	49 (46.2)	18 (48.6)
Toxicity (%)	29 (27.4)	9 (24.3)

*P<0.0001.

according to the psychologist's judgement (p=0.01) and reading the leaflet (p=0.03).

Parental decision-making process

Median (IQR) period of reflection before consent was 4.8 (1–7) days. Seventy (58.8%) parents did not want to take any additional time.

Table 3 Has information regarding the early phase trial been delivered to the child? Measurements according to the various perspectives

	According to the physicians (n=93)	According to the parents (n=119)	According to the child (n=37)
Systematic sharing of information with the child (%)	69 (74.2)	60 (50.4)	22 (59.5)
Information given by:			
Physician only (%)	42 (45.2)	7 (5.9)	20 (54.1)
Parents only (%)	0	6 (5)	1 (2.7)
Physician and parents together (%)	26 (27.9)	43 (36.1)	1 (2.7)
Missing data (%)	1 (1.1)	4 (3.4)	0
No delivery of information (%)	24 (25.8)	59 (49.6)	15 (40.5)
Children age in years, median (IQR)	3.9 (3.3–5.5)	9.5 (5.5–13.6)	11.2 (10–12.7)

To the question 'How did you experience having to make a decision?' the answers were: the obviousness to participate (n=70, 58.8%), the feeling that they had no choice (n=62, 52.1%), the difficulty of the decision-making (n=21, 17.6%) and the hesitation until the last moment (n=12, 10.1%). Regarding the elements underlying their decisions, the answers were: the confidence in the medical team (n=60, 50.4%), the belief that it was the best and/or unique treatment (respectively n=47, 39.5% and n=45, 37.8%), the belief that there were more benefits than risks (n=20, 16.8%) and the possibility to stop at any time (n=20, 16.8%).

Children's decision-making process

Fifty (42%) parents of 44 children acknowledged their child's involvement in the decision. According to the parents, their participation consisted of taking part in the final decision (n=34/50), or in giving their opinion (n=14/50). They had a median (IQR) age of 13.3 (11.2–14.7) years.

According to the children, 26 (70.3%) of them participated in the decision-making process. This participation was recognised by their parents and/or physicians. Their involvement consisted of: taking part in the final decision (n=12, median age 15.1), giving their opinion (n=5, median age 13.5 years) and making the decision on their own (n=2, children aged 17 years enrolled without their parents). The children involved in the decision were older than those who did not get involved, with a median (IQR) age of 14.5 (12.3–17) years vs 11 (9.5–12) years, p=0.004.

Among these 26 children, 18 answered on their personal experience and could give several answers. Ten thought that it was obvious to participate in the trial, six felt that they had no choice, three were hesitant until the last moment and three thought it was a difficult decision. Regarding the elements underlying their decision, the answers were: the belief that it was the best and/or unique treatment (respectively n=9 and n=6), the belief that there were more benefits than risks (n=6), the collective benefit (n=5), the possibility to stop at any time (n=5) and the confidence in the medical team (n=4).

DISCUSSION

Most parents understood the general aspects of the consent information (eg, nature of the research, settings of the trial, right to withdraw). By contrast, less than half of the parents correctly understood the more specific information, namely the individual benefits, risks and alternative options. Regarding the prospects of individual benefits, almost half of the parents mentioned the hope for a cure. In phase I studies, it is essential to draw a distinction between research objectives (toxicity, recommended dose determination) and the personal objectives of the patient/parent/caregiver, which are mainly related to the hope for a tumour response. The reason for this hope (therapeutic misconception) may be in the delivering of information. Hazen *et al* showed that in phase I oncology trial, risks and benefits were presented respectively to 95% and 88% of the families.[12] On the contrary, Miller *et al* showed that the risk of death from the disease was only addressed in approximately 15% of IC conferences.[13] Regarding the alternatives, parents in the present study rarely mentioned the purely palliative care aspect, and the early phase trial was considered as the unique option for a third of the parents. Careful communication is essential and a benevolent attention is required.[14 15] To improve the quality of discussions, Johnson *et al* proposed to start addressing research participation at the time of diagnosis, and to complete information at each important decision point throughout the child's care journey.[16]

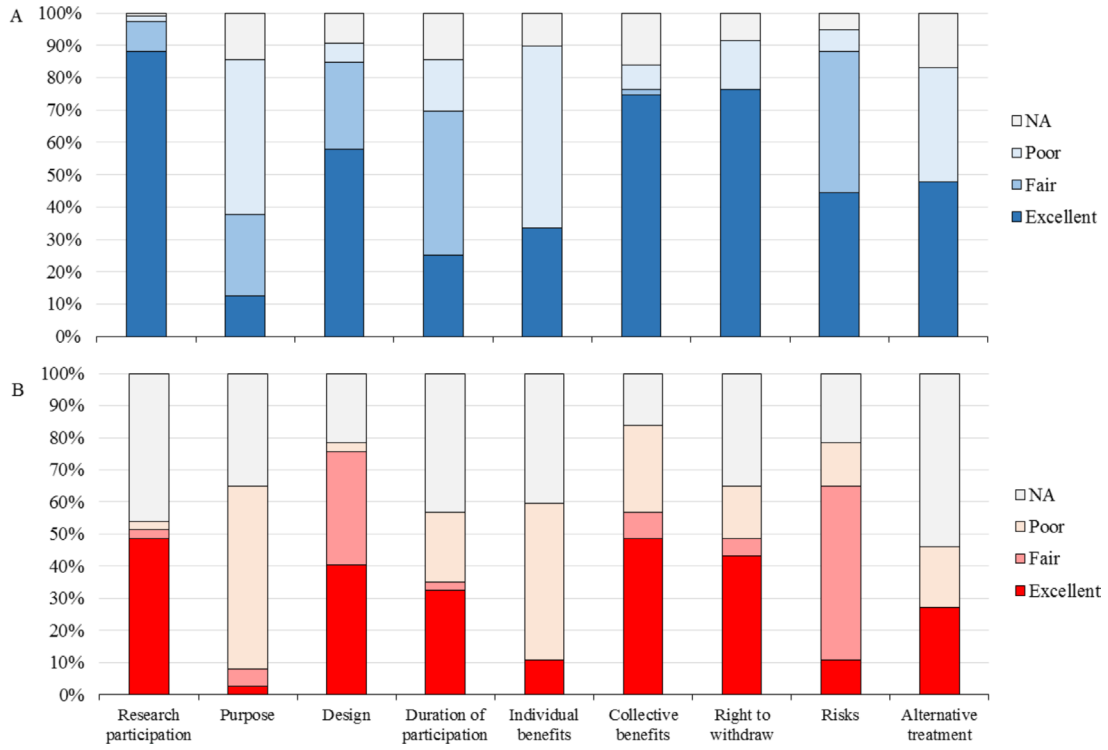

Figure 2 Comprehension of the nine elements of the informed consent for all the parents (A) and children (B). Missing data (elements not evaluated during the interview) were graded NA (not available).

Overall, even if the decision was difficult, more than half of the parents in this study considered participation in the trial as obvious. This decision was bound to their confidence in the medical team. Although parents were not induced by the physicians to consent, they mostly felt like they had no choice. Maurer *et al* already showed that parents who chose to participate in an early phase oncology trial often felt compelled, whereas parents who opted for palliative care explicitly privileged the quality of life of their child.[17] A Canadian study found two factors having an impact on the choice between an early phase trial and palliative care: quality of life and remaining lifespan.[18] In other studies, parents favoured early phase trial based on hope.[19–21] Hope for a tumour response or for a cure alleviates the difficulty for the parents to accept the clinical trial.

The present findings furthermore revealed that children did not systematically receive information regarding the early phase trial, due in part to their young age. Like their parents, their understanding was good for the general aspects, but inadequate for the specific elements of the trial. They had a better understanding of the right to withdraw if they were older than 15 years old and if they had read the leaflet, in concordance with our previous results.[22] According to Baker *et al*, parents and children suggested ways to improve IC: sufficient time dedicated to deliver individual detailed information, provision of detailed information, especially for the most frequent and severe risks, and some information regarding the progress of the trial.[23]

Almost three-quarters of the children herein acknowledged their active participation in the decision-making process, that is, to share their opinion, or to take part in the decision. There are very little data in the literature regarding the child's decision, hence warranting further study relative to their role.[24] Even when the child takes part in the decision, adult responsibility remains important.[25] The challenge for the investigator is to assess the age or developmental level at which information should be delivered, and affirmative agreement should be sought. Hein *et al* showed that a child's competence to assent for clinical research was obtained when he/she was older than 11.2 years.[26] However, physicians often hold teenagers as incompetent to involve in discussions regarding research, and therefore refrain from providing the latter with all of the necessary information.[27] A study by Swartling *et al* furthermore showed that parents shared the same mindset.[28] Indeed, the parents did not want to involve their child in the decision, assuming that they lacked the competence and accurate comprehension. Moreover, their autonomy and capacity to make decisions were not considered. However, in a study involving adolescents and young adults participating in phase I trial, 85% of the patients deemed that they themselves had made the decision.[29] Factors affecting their decision were their quality of life, prospects of additional lifespan and individual benefits, and measures to minimise risks.

Our study has certain limitations. The first is the delay in meeting the families, with the possibility that some information was repeated or explained anew in the meantime. A second limitation is the absence of the physicians' perspective regarding the delivery of information. In addition, the physicians partly selected the included families, as families were not asked to participate in this study. Finally, study settings should also be considered. For example, respondents might be reluctant to address a risk of death during the course of the interview, which may possibly lead to underestimate their understanding of this key element of consent.

CONCLUSIONS

Although the parents' and children's understanding is poor for some important concepts of consent, it might be sufficient for the parents to make a decision. Moreover, some parents are willing to include their child in the decision. We should ensure

that all children (excluding infants) are able to be informed and to give their opinion in order to ensure their meaningful involvement in research.

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Contributors AB analysed and interpreted the data, and drafted the initial manuscript. NB analysed the data, and reviewed and revised the manuscript. AdHdS and ACFW contributed to the design of the study, designed the data collection instruments, implemented the study, acquired and analysed the data, and reviewed and revised the manuscript. DD contributed to the design of the study, designed the data collection instruments, and reviewed and revised the manuscript. IA, BG, AA, BB, PL, NC, NA and HM coordinated and supervised the data collection, and reviewed and revised the manuscript. JCKD interpreted the data, and reviewed and revised the manuscript. FD contributed to the design of the study, designed the data collection instruments, coordinated and supervised the data collection, and reviewed and revised the manuscript. CH was the principal investigator of the study, contributed to the design, designed the data collection instruments, implemented the study, coordinated and supervised the data collection, analysed and interpreted the data, and reviewed and revised the manuscript. All authors critically reviewed iterations of the report and approved the final draft for submission.

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