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Improved parental understanding in a pediatric drug trial by an enhanced informed consent form: a randomized controlled study

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TITLE PAGE

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Key words: Informed consent; Parental consent; Pediatrics; Consent forms; Comprehension.

Abstract

Objective: This study aimed to evaluate the applicability and effectiveness of the enhanced informed consent form (ICF) methodology, proposed by the Strategic Initiative for Developing Capacity in Ethical Review (SIDCER), in pediatric research requiring parental consent.

Design: A prospective, randomized-controlled design.

Setting: Pediatric Outpatients Department, Phramongkutklao Hospital, Thailand.

Participants: 210 parents of children with thalassemia.

Interventions: The participants were randomly assigned to read either the SIDCER ICF (n = 105) or the conventional ICF (n = 105) of a pediatric drug trial.

Primary and secondary outcome measures: Parental understanding of trial information was determined using 24 scenario-based questions. The primary endpoint was the proportion of parents who obtained the understanding score of more than 80%, and the secondary endpoint was the total score.

Results: Forty-five parents (42.9%) in the SIDCER ICF group and 29 parents (27.6%) in the conventional ICF group achieved the primary endpoint (relative risk = 1.552, 95%CI = 1.061 to 2.270, p = 0.021). The median total scores of the parents in the SIDCER ICF group and in the conventional ICF group were 19/24 and 17/24, respectively (p = 0.001).

Conclusions: The SIDCER ICF was found to be superior to the conventional ICF in improving parental understanding of several elements of the ICF content. Further improvement on the ICF for this group of population is required as deficiencies in understanding were still prevalent.

Strengths and limitations of the study

- This randomized-controlled study provides evidence that an informed consent form (ICF) for parental consent of pediatric research could be improved, using the SIDCER ICF methodology.
- This study was confined to parental understanding of ICFs while children's understanding of an assent form was not studied.
- The findings were largely confined to research contexts in Thailand and may not account for other settings.

Introduction

In pediatric research, enrollment of child subjects generally requires parental permission.[1] Adequate parental understanding of trial information is one of the keys to the ethical conduct of pediatric research because informed parents can act, as proxy decision makers, in their child's best interests and protect their child from assuming unreasonable risks.[2] Despite increasing ethical and regulatory scrutiny, deficiencies still exist in parental understanding; some parents have consented to research unaware of the experimental nature of research and the risks involved, or even the fact that they have consented to research on behalf of their child.[3-7] This is of ethical concern because inadequate parental understanding could jeopardize the safety and interest of a child subject and render him/her even more vulnerable.

An informed consent form (ICF) serves as a mandatory document for disclosure of research information to the subjects and/or their surrogate decision makers. Although the form alone may not be sufficient to achieve a proper, valid consent, it can and do serve multiple purposes in clinical trials, including the assurance of complete disclosure of information and enhancement of participants' comprehension.[8] In theoretical ideal, an ICF given to parents in pediatric research should be complete, concise, and understandable so that it would enable them to come to an informed decision in regard to their child's participation in a study.[9] In reality, empirical observations reveal a number of lengthy, detailed, and complicated ICFs which are unlikely to be read and understood by general laypersons.[10-12] Most ICF templates

still seem to require a high level of reading comprehension.[13] The written language in quite a few ICFs stems from a desire to provide legal protection to investigators and sponsors rather than one designed to inform participants/surrogates for rational decision making.[14] At present, there is wide agreement that informed consent (including parental permission) requires more than a signature on a form: efforts should be put to promote understanding of consent information.[15]

The Strategic Initiative for Developing Capacity in Ethical Review (SIDCER) has recently proposed the 'enhanced ICF development' methodology, named 'SIDCER ICF', in response to the need for making an ICF complete, concise and understandable.[16] The SIDCER ICF methodology has been tested in real informed consent settings involving several clinical trials and it has been shown to be effective in improving participants' understanding.[17] It is compelling to extend the application of the SIDCER ICF methodology to clinical research requiring proxy consent. The present study was, thus, designed to test the applicability and effectiveness of the SIDCER ICF in pediatric research requiring parental consent.

Materials and Methods

This randomized-controlled study compared the effectiveness of two different ICFs – the SIDCER ICF and the conventional ICF (1:1) – on parental understanding of research-related information. The study protocol and related documents obtained ethical approval from the Institutional Review Board of Royal Thai Army Medical Department.

Study participants

Parents of children with transfusion-dependent thalassemia were recruited at the Pediatric Outpatients Department, Phramongkutklao Hospital, Bangkok, Thailand. They were invited to read either the SIDCER ICF or the conventional ICF (by random assignment) for possible enrollment of their child in a drug trial[18]; any refusal to read an ICF given was respected. This ICF study planned to enroll 210 parents (with 105 parents in each arm), based on an *a priori* estimate to detect the hypothesized effect size of 20% difference between two independent proportions of the primary endpoint ($p_1 = 0.8$ and $p_2 = 0.6$), with the precision and confidence level of 95%, 80% power and allocation ratio of 1, with a continuity correction.

Study interventions

The effectiveness of two different ICF interventions on parental understanding were compared: one was the original, standard ICF of the pediatric drug trial (in Thai) and another was the enhanced (SIDCER) ICF of the trial (in Thai). The former comprising six pages with 2,065 words was considered as the conventional ICF; trial-related information was described

using text in standard sequences. The latter comprising four pages with 1,644 words was developed according to the SIDCER ICF principles and template, comprehensively described elsewhere.[15] The SIDCER ICF contained complete and concise information of the drug trial in an enhanced format using summary boxes, highlights, and illustrations, when appropriate.

Study outcomes

Parental understanding of essential research-related information was measured using the questionnaire (in Thai). It consisted of 24 scenario-based questions, aimed at assessing parental understanding of 24 required elements of the ICF content: five elements on general aspects, four elements on right aspects, eight elements on scientific aspects, and seven elements on ethical aspects. Of three possible answers in each question, there was only one correct answer, counting as a score of 1, making the total score 24. The primary endpoint was the proportion of parents obtaining the total score of more than 80% (≥20/24). The secondary endpoints were the total score, the score of each categorical aspect, and time spent reading a given ICF and completing the questionnaire.

Study procedure

Simple randomization was applied, and a randomization code was generated and packed in an opaque sealed envelope before subject enrollment to this ICF study. Eligible parents were randomly assigned to read either the SIDCER ICF or the conventional ICF. After that, the questionnaire was distributed. The parents could keep and read the ICF while

completing the questionnaire, but they could not ask any questions during this process. Time spent reading the given ICF and completing the questionnaire was recorded and this was the end of the ICF study. The informed consent process continued for the clinical trial for both groups in the same manner, that is, informed consent discussion with the parents was conducted and any inaccurate understanding of trial information was explained prior to the parents' decision whether or not to sign consent for their child's participation in a pediatric drug trial.

Data analysis

Descriptive statistics were used to describe the basic features of the data in this study. Dichotomous variables were compared using χ^2 test or Fisher's exact test, as appropriate, and continuous variables were compared using nonparametric statistics (*i.e.*, the Wilcoxon rank-sum test). The proportion of the parents in the SIDCER ICF group who achieved the outcome divided by that of the conventional ICF group was presented using the term 'relative risk (RR)'. Subgroup analysis was done to determine the impact of gender, age and education on the primary endpoint. Multivariable logistic regression analysis was performed to obtain odds ratio (OR), a measure of association between demographic variables and the primary outcome. All statistical analysis was executed using IBM SPSS Statistics for Windows, Version 22.0, with a p value of less than 0.05 considered to indicate statistical significance.

Results

Two hundred and ten parents of thalassemia children were enrolled between September 2015 and September 2016 and equally assigned to the SIDCER ICF group (n = 105) and the conventional ICF group (n = 105). The mean age of 210 enrolled parents was 35.6 (±3.1) years; 72.9% were female, and 61.0% had education at a bachelor degree or higher (Table 1).

The primary endpoint was achieved by 42.9% and 27.6% of the parents in the SIDCER ICF group and the conventional ICF group, respectively (RR = 1.552, 95%CI = 1.061 to 2.270, p = 0.021) (Fig. 1). The superiority of the SIDCER ICF over the conventional ICF in improving parental understanding was seen particularly among those aged more than 35 years and those whose education was at a bachelor degree or higher (RR = 1.986, 95%CI = 1.193 to 3.305, p = 0.006; RR = 1.870, 95%CI = 1.234 to 2.834, p = 0.003, respectively) (Fig. 1). The multivariable analysis demonstrated that female gender and education at a bachelor degree or higher were independently associated with higher attainment of the primary endpoint (OR = 2.213, 95%CI = 1.067 to 4.591, p = 0.033; OR = 2.052, 95%CI = 1.093 to 3.852, p = 0.025), whereas age of the parents was not (OR = 1.008, 95%CI = 0.985 to 1.031, p = 0.485).

The values of the secondary endpoints of this study are presented in Table 2. The parents in the SIDCER ICF group obtained higher total scores in less time spent when compared to the conventional ICF group (total score: 19 *vs*. 17, p = 0.001; time spent reading

an ICF: 20 min *vs*. 30 min, $p < 0.001$). Proportions of the parents who correctly answered each element of the ICF content were compared between the two groups. The SIDCER ICF was found to be superior to the conventional ICF in improving parental understanding on five elements: who can access the data, right to receive new information, identification of experimental procedures, alternative course of treatment, and number of subjects required (Table 3). The element that was least understood by the parents in both groups was trial treatment and random assignment; only 66 (out of 210) parents (31.4%) answered this element correctly.

Discussion

The present study demonstrated that the understanding level of trial information was significantly greater among parents who read the SIDCER ICF, when compared to those who read the conventional ICF. This indicates the applicability and effectiveness of the SIDCER ICF methodology in improving parental understanding of trial information in pediatric research requiring parental permission. The overall results of this study are consistent with three previous, independent informed consent studies that exhibited the improvement of participants' understanding by the SIDCER ICF.[17,19,20] In line with a recent integrative review on informed consent, enhanced ICFs associated with improved understanding are generally concise, context-specific, and simple, with increased processability (using summary boxes, highlights, and illustrations, when appropriate) to be more accessible and easily understood by readers.[21] All these characteristics make the SIDCER ICFs more readable and comprehensible, as consistently demonstrated in multiple studies.[17,19,20]

Two factors – education and gender of the parents – were identified to be an independent predictor of parental understanding levels of trial information in this study. Based on empirical observation, higher educational background is commonly found to be a major determinant of a greater understanding of information.[22,23] Researchers and ethics committee members should, thus, pay particular attention to the adequacy of understanding when proposed research involves participants or parents with a limited academic background, that is,

the language used in the ICF must suit the individual's level of understanding. In addition, the present study identified another feature associated with understanding levels of trial information; female parents obtained optimal comprehension of trial information in a higher proportion than male parents did. Although it was unclear to us why female parents did better than male parents, one hypothesis to explain this observation is that women in general might be more information-seeking and tended to read the ICF more thoroughly than men. Female parents might have had more concern about their child's participation in research or might have taken more responsibility of the child's health care than did male parents, so they were more likely to read the ICF and contemplate the information more seriously.[24] However, a relatively few male parents in this study might not be a suitable representative of their group.

Close examination of the data revealed that the SIDCER ICF was superior to the conventional ICF in increasing the parental understanding of trial information in five elements. First, 'who can access the data'; it is important that the parents should understand the limit of confidentiality of their child's health data, so they would not incorrectly assume their child's health information to be fully kept confidential. This is due to the fact that some authority persons (*e.g.*, the monitors or the regulatory authorities) may be granted direct access to the subject's original medical records as required by regulations. Second, 'right to receive new information'; this element emphasized the nature of informed consent as an ongoing, interactive process. The parents should know that informed consent does not end when they

sign the consent form; rather, they would still be kept informed of any new, relevant information that may become available and affect their decision during the course of the trial. Third, 'identification of experimental procedures'; this element could help parents distinguish the procedures that are experimental in the trial from those used in routine care and recognize that research is not the same as standard care.[25] The additional risks derived from experimental procedures should be understood and accepted by the parents before they let their child participate in a trial. Fourth, 'alternative course of treatment'; this element provided information about other options that the child would have had if his/her parents decided not to let him/her participate in the study. Understanding of this element would ensure the voluntariness of trial participation. The parents should recognize that trial participation is not the only option available for their child. Fifth, 'number of subjects required'; this element informed parents about the approximate number of children that the trial would recruit. This information could be material to decision making for trial participation in some settings; for example, some parents may be reluctant to let their child participate in a trial involving a small number of children, while they may feel more comfortable when a trial involves a large number of subjects with the same condition as their child.

The element that was least understood by the parents in both groups was 'trial treatment and random assignment'. This finding supports lines of the evidence demonstrating that there is the apparent universality of a limited understanding on the aspect of random

allocation of the intervention in clinical trials.[26-27] Despite an attempt with increased processability in the SIDCER ICF to aid in description on the concept of randomization (using illustrations and highlights), a large proportion of the parents (63.8%) still did not understand it accurately. This emphasizes the need of increased attention in particular during informed consent discussion to ensure adequate understanding of this concept among individuals who consent to a trial.[28] A combination of the SIDCER ICF methodology with other means (*e.g.*, an integrated cognitive approach[29]) may enhance parental understanding of consent information in pediatric research.

Although the overall results demonstrated that the SIDCER ICF was proven superior to the conventional ICF, the degree of parental understanding remained unsatisfactory. Deficiencies in understanding were still prevalent even among those who read the SIDCER ICF. Truong *et al* observed that parents of children with poor prognoses seem to understand trial information better than do parents of children with more favorable prognoses.[30] Continued consideration of the normative and practical aspects of informed consent is needed in an attempt to facilitate understanding among parents who act as proxies for their child's participation in research.[31,32] It may be worthwhile to consider using more graphics or pictographs to enhance visualization of complex information,[33] and further research may be required to determine the effectiveness of such additional means in this group of population. A dialogue between the investigator (or a person designated by the investigator) and the parents

are still indispensable, while complimentary methods of delivering trial-related information (*e.g.*, a multimedia video and website[29]) may be warranted in some studies. Furthermore, formal evaluation of parental understanding during the process of informed consent may be necessary in pediatric research that poses relatively high risks, with little or no potential direct benefit, to child subjects.[34,35] Accordingly, any inaccuracy of parental understanding could be rectified to ascertain the validity of parental consent obtained in such research.

Of note, this study was confined to parental understanding of ICFs while children's understanding of an assent form was not studied. It is also possible that the SIDCER ICF methodology may be modified and used to improve the quality of assent forms for pediatric populations. As such, further ICF studies involving pediatric populations are warranted.

In conclusion, the present study demonstrated that the SIDCER ICF methodology was applicable to pediatric research requiring parental consent and effective in improving parental understanding of trial information. However, deficiencies in understanding were still prevalent among the parents of child subjects, at least, in this setting, suggesting that further research is required to improve parental understanding in pediatric drug trials.

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Contributor: The study was designed by Nut Koonrungsesomboon and Juntra Karbwang, and conducted by Chanchai Traivaree and Charnunnut Tiyapsane. Data analysis was done by Nut Koonrungsesomboon. The manuscript was written by Nut Koonrungsesomboon and revised by Juntra Karbwang, with contributions from all authors. All authors approved the final version submitted.

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Competing interests: We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

Ethics approval: This study was approved by …

Data sharing statement: The participants did not give consent for data to be shared beyond the research team.

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Table 1 Demographic data of the parents (n = 210)

	SIDCER ICF (n = 105)	Conventional ICF (n = 105)
Gender		
Male	30 (28.6%)	27 (25.7%)
Female	75 (71.4%)	78 (74.3%)
Age		
<35 years	58 (55.2%)	49 (46.7%)
≥35 years	47 (44.8%)	56 (53.3%)
Education		
High school or below	49 (46.7%)	33 (31.4%)
Bachelor degree or above	56 (53.3%)	72 (68.6%)

Data represent the number of parents. ICF, informed consent form.

Table 2 The total score, the score in each categorical aspect of the ICF content, and time spent reading a given ICF and completing the questionnaire

	SIDCER ICF (n = 105)	**Conventional ICF** (n = 105)	***p***
Total score (out of 24)	19 (16 to 21)	17 (12 to 20)	**0.001**
- Score in the general aspects (out of 5)	4 (3 to 5)	4 (3 to 5)	0.080
- Score in the rights aspects (out of 4)	4 (3 to 4)	4 (2 to 4)	0.502
- Score in the scientific aspects (out of 8)	5 (4 to 7)	5 (3 to 6)	**<0.001**
- Score in the ethical aspects (out of 7)	5 (4 to 7)	5 (3 to 6)	**0.015**
Time spent reading a given ICF (minutes)	20 (15 to 30)	30 (20 to 30)	**<0.001**
Time spent completing the questionnaire (minutes)	20 (15 to 30)	30 (20 to 35)	**<0.001**

Data represent median (interquartile range, Q_1 to Q_3).

364 **Table 3** Parental understanding in each element of the ICF content

	SIDCER ICF (n = 105)		Conventional ICF (n = 105)		Relative Risk (95%CI)		p
General aspects							
1. Recognition that this is research	80	(76.2%)	78	(74.3%)	1.026	(0.878-1.198)	0.749
2. Subjects' responsibility	85	(81.0%)	84	(80.0%)	1.012	(0.886-1.156)	0.862
3. Confidentiality of records	74	(70.5%)	64	(61.0%)	1.156	(0.950-1.408)	0.146
4. Who can access the data	82	(78.1%)	68	(64.8%)	1.206	(1.014-1.435)	**0.032**
5. Research contact persons	98	(93.3%)	96	(91.4%)	1.021	(0.944-1.103)	0.603
Right aspects							
6. Right to refuse	76	(72.4%)	87	(82.9%)	0.874	(0.754-1.012)	0.069
7. Right to withdraw	95	(90.5%)	87	(82.9%)	1.092	(0.981-1.215)	0.104
8. Consequences of withdrawal	96	(91.4%)	87	(82.9%)	1.103	(0.994-1.225)	0.064
9. Right to receive new information	91	(86.7%)	78	(74.3%)	1.167	(1.019-1.336)	**0.024**
Scientific aspects							
10. Eligibility of the subject	81	(77.1%)	72	(68.6%)	1.125	(0.953-1.328)	0.163
11. Number of subjects required	87	(82.9%)	43	(41.0%)	2.023	(1.583-2.587)	**<0.001**
12. Purpose of the study	80	(76.2%)	75	(71.4%)	1.067	(0.908-1.254)	0.433
13. Trial treatment and random assignment	38	(36.2%)	28	(26.7%)	1.357	(0.904-2.038)	0.137
14. Trial procedures	65	(61.9%)	52	(49.5%)	1.250	(0.979-1.596)	0.071
15. Identification of experimental procedures	80	(76.2%)	66	(62.9%)	1.212	(1.011-1.454)	**0.036**
16. Duration of the subject's participation	88	(83.8%)	79	(75.2%)	1.114	(0.970-1.279)	0.124
17. Storage and reuse of human materials	60	(57.1%)	57	(54.3%)	1.053	(0.827-1.340)	0.677
Ethical aspects							
18. Alternative course of treatment	94	(89.5%)	82	(78.1%)	1.146	(1.016-1.293)	**0.025**
19. Foreseeable risks	70	(66.7%)	61	(58.1%)	1.148	(0.929-1.418)	0.200
20. Expected direct/indirect benefits	52	(49.5%)	42	(40.0%)	1.238	(0.914-1.677)	0.165
21. Post-trial benefits	82	(78.1%)	72	(68.6%)	1.139	(0.966-1.342)	0.119
22. Prorated payment for participation	91	(86.7%)	84	(80.0%)	1.083	(0.959-1.223)	0.195
23. Anticipated expenses	60	(57.1%)	53	(50.5%)	1.132	(0.880-1.456)	0.333
24. Compensation for injury	92	(87.6%)	83	(79.0%)	1.108	(0.981-1.252)	0.096

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Figure legends

Fig. 1 Proportions of the parents whose understanding score was more than 80% (≥20/24)

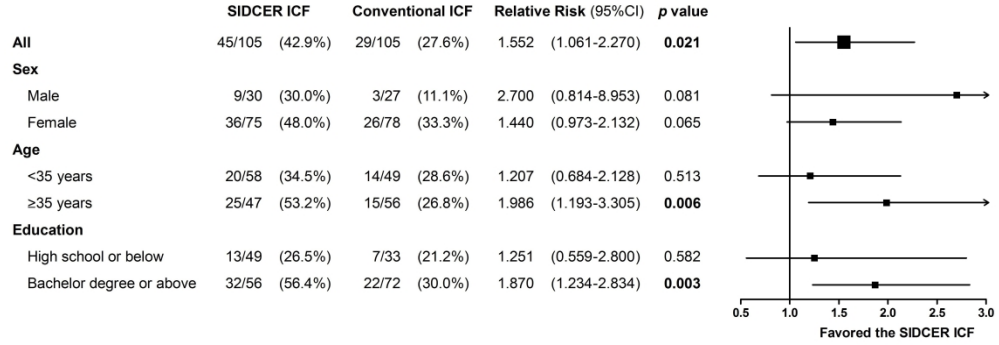

Fig. 1 Proportions of the parents whose understanding score was more than 80% (≥20/24)

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2-3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	5-6
	2b	Specific objectives or hypotheses	6
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	7
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	n/a
Participants	4a	Eligibility criteria for participants	7
	4b	Settings and locations where the data were collected	7
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7-8
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8
	6b	Any changes to trial outcomes after the trial commenced, with reasons	n/a
Sample size	7a	How sample size was determined	7
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n/a
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	8
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	8
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	8
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	8

Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	n/a
	11b	If relevant, description of the similarity of interventions	n/a
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	9
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	9
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	10
	13b	For each group, losses and exclusions after randomisation, together with reasons	n/a
Recruitment	14a	Dates defining the periods of recruitment and follow-up	10
	14b	Why the trial ended or was stopped	n/a
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	10
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	10-11, Fig. 1
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	10-11, Fig. 1
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	10-11
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	n/a
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	12-16
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	12-16
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	12-16
Other information			
Registration	23	Registration number and name of trial registry	n/a
Protocol	24	Where the full trial protocol can be accessed, if available	n/a
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	17

n/a, not applicable

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Improved parental understanding by an enhanced informed consent form: a randomized controlled study nested in a pediatric drug trial

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TITLE PAGE

Title: Improved parental understanding by an enhanced informed consent form: a randomized controlled study nested in a pediatric drug trial

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Key words: Informed consent; Parental consent; Pediatrics; Consent forms; Comprehension.

Abstract

Objective: This study was designed to evaluate the applicability and effectiveness of the enhanced informed consent form (ICF) methodology, proposed by the Strategic Initiative for Developing Capacity in Ethical Review (SIDCER), in pediatric research requiring parental consent. The objective of this study was to compare the parental understanding of information between the parents who read the SIDCER ICF and those who read the conventional ICF.

Design: A prospective, randomized-controlled design.

Setting: Pediatric Outpatients Department, Phramongkutklao Hospital, Thailand.

Participants: 210 parents of children with thalassemia (age = 35.6 ± 13.1 years).

Interventions: The parents were randomly assigned to read either the SIDCER ICF (n = 105) or the conventional ICF (n = 105) of a pediatric drug trial.

Primary and secondary outcome measures: Parental understanding of trial information was determined using 24 scenario-based questions. The primary endpoint was the proportion of parents who obtained the understanding score of more than 80%, and the secondary endpoint was the total score.

Results: Forty-five parents (42.9%) in the SIDCER ICF group and 29 parents (27.6%) in the conventional ICF group achieved the primary endpoint (relative risk = 1.552, 95%CI = 1.061 to 2.270, p = 0.021). The total score of the parents in the SIDCER ICF group was significantly higher than the conventional ICF group (18.07 ± 3.71 *vs*. 15.98 ± 4.56, p = 0.001).

Conclusions: The SIDCER ICF was found to be superior to the conventional ICF in improving parental understanding of trial information.

Strengths and limitations of the study

- This study was a comparative, randomized-controlled study, in which the SIDCER ICF (study intervention) was directly compared to the conventional ICF (control) to establish superiority.
- This study was conducted on actual parents deciding whether or not to allow their child to participate in a pediatric drug trial.
- This study was confined to the parental understanding of an ICF while the child's understanding of an assent form was not studied.
- The findings were largely confined to research contexts in Thailand and may not account for other settings.

Introduction

In pediatric research, enrollment of child subjects generally requires parental permission.[1] Adequate parental understanding of trial information is one of the keys to the ethical conduct of pediatric research because informed parents can act, as proxy decision makers, in their child's best interests and protect their child from assuming unreasonable risks.[2] Despite increasing ethical and regulatory scrutiny, deficiencies still exist in parental understanding; some parents have consented to research without understanding the experimental nature of it and the risks involved, or even that they are consenting on behalf of their child.[3-7]

An informed consent form (ICF) serves as a mandatory document to provide trial relevant information to the participants/surrogate decision makers and document their consent; it consists of the information sheet and the consent certificate. Although the form alone may not be sufficient to achieve a proper, valid consent, it can and do serve multiple purposes in clinical trials, including the assurance of complete disclosure of information and enhancement of participants' comprehension.[8] Ideally, an ICF given to parents in pediatric research should be complete, concise, and understandable so that it would enable them to come to an informed decision in regard to their child's participation in a study.[9] In reality, empirical observations reveal a number of lengthy, detailed, and complicated ICFs which are unlikely to be read and understood by general laypersons.[10-12] Most ICF templates still seem to require a high level of

reading comprehension.[13] It has been suggested that the written language in quite a few ICFs stems from a desire to provide legal protection to investigators and sponsors rather than one designed to inform participants/surrogates for rational decision making.[14] At present, there is wide agreement that informed consent (including parental permission) requires more than a signature on a form: efforts should be put to promote understanding of consent information.[15]

The Strategic Initiative for Developing Capacity in Ethical Review (SIDCER) has recently proposed the 'enhanced ICF development' methodology, named 'SIDCER ICF', in response to the need for making an ICF complete, concise and understandable.[16] The SIDCER ICF methodology has been tested in real informed consent settings involving several clinical trials and it has been shown to be effective in improving participants' understanding.[17] As such, it is compelling to extend the application of the SIDCER ICF methodology to clinical research requiring proxy consent. Therefore, the present study was designed to test the applicability and effectiveness of the SIDCER ICF in pediatric research requiring parental consent. The objective of this study was to compare the parental understanding of information between the parents who read the SIDCER ICF and those who read the conventional ICF.

Materials and Methods

This open-label, comparative, randomized-controlled study determined the effectiveness of two different ICFs – the SIDCER ICF and the conventional ICF (1:1) – on parental understanding of research-related information. The study protocol and related documents obtained ethical approval from the Institutional Review Board of Royal Thai Army Medical Department.

Study participants

Parents of children with transfusion-dependent thalassemia were informed about this ICF study and were recruited by study nurse at the Pediatric Outpatients Department, Phramongkutklao Hospital, Bangkok, Thailand. They were invited to read either the SIDCER ICF or the conventional ICF (by random assignment) for possible enrollment of their child (aged 1-18 years) in a drug trial which investigated the effects of furosemide on markers of volume overload in children with transfusion-dependent thalassemia.[18] Informed consent was obtained verbally and by action, provided that answering the questionnaire inferred their consent for participation in this ICF study.

This ICF study planned to enroll 210 parents (with 105 parents in each arm), based on an *a priori* estimate to detect the hypothesized effect size of 20% difference between two independent proportions of the primary endpoint ($p_1 = 0.8$ and $p_2 = 0.6$), with the precision and confidence level of 95%, 80% power and allocation ratio of 1, with a continuity correction.

This hypothesized effect size was based on the findings in our previous study.[19]

Study interventions

The effectiveness of two different ICF interventions on parental understanding were compared: one was the original, standard ICF of the pediatric drug trial (in Thai) and another was the enhanced (SIDCER) ICF of the trial (in Thai). The former comprising six pages with 2,065 words was considered as the conventional ICF; trial-related information was described using text in standard sequences. The latter comprising four pages with 1,644 words was developed according to the SIDCER ICF methodology, comprehensively described elsewhere.[16] In brief, essential information as is relevant to the parents' decision making was summarized in the SIDCER ICF template (available from http://ijme.in/pdf/appendix-1.pdf?v=1) in a narrative and illustrative manner, according to the SIDCER ICF principles. The drafted SIDCER ICF was, then, reviewed by laypersons to enhance the readability and understandability of written information. Both conventional and SIDCER ICFs contained the same content.

Study outcomes

Parental understanding of essential research-related information was measured using the questionnaire (in Thai), which was modified from our previous studies.[17,19,20] It consisted of 24 scenario-based questions which assessed parental understanding of relevant ICF content in the following categories: general items (five questions), patient's rights (four questions),

scientific aspects (eight questions), and ethics aspects (seven questions). Each question with three possible answers was structured in a way that the parents would have had to apply their understanding of information given in an ICF to the scenario.[21] In each question, there was only one correct answer, counting as a score of 1, making the total score 24. The primary endpoint was the proportion of parents obtaining the total score of more than 80% (≥20/24). The secondary endpoints were the total score, the score of each category, and time spent reading a given ICF and completing the questionnaire.

Study procedure

For allocation of the parents, a computer-generated list of random numbers was applied, and a randomization code was packed in an opaque sealed envelope before subject enrollment to this ICF study. Eligible parents were randomly assigned to read either the SIDCER ICF or the conventional ICF. After that, the questionnaire was distributed. The parents could keep and read the ICF while completing the questionnaire, but they could not ask any questions during this process. Time spent reading the given ICF and completing the questionnaire was recorded and this was the end of the ICF study. The informed consent process continued for the clinical trial for both groups in the same manner, that is, informed consent discussion with the parents was conducted and any inaccurate understanding of trial information was explained prior to the parents' decision whether or not to sign consent for their child's participation in the pediatric drug trial.

Participant and public involvement

The present study did not involve participants or publics during the development of research question and outcome measures as well as in the study design and recruitment plan. Participant burden was not assessed formally, but assumed to be low. Results will be disseminated via this publication, with a lay summary of the results in Thai.

Data analysis

Descriptive statistics were used to describe the basic features of the data in this study. The proportion of the parents in the SIDCER ICF group who achieved the outcome divided by that of the conventional ICF group was presented using the term 'relative risk' (RR). Dichotomous variables were compared using χ^2 test or Fisher's exact test, as appropriate. Continuous variables were presented in mean ± standard deviation (SD), and the values between the two groups were compared using the Student *t*-test. Cohen's *d* was used to classify the effect size as small ($d = 0.2$), medium ($d = 0.5$), and large ($d = 0.8$).[22] Multivariable linear regression analysis was performed to evaluate the relationship between different ICF interventions and the total score after adjusting for age, gender, and education. All statistical analysis was executed using IBM SPSS Statistics for Windows, Version 22.0, with a *p* value of less than 0.05 considered to indicate statistical significance.

Results

Two hundred and ten parents of thalassemia children were enrolled between September 2015 and September 2016 and equally assigned to the SIDCER ICF group (n = 105) and the conventional ICF group (n = 105) (Fig. 1). The mean age of 210 enrolled parents was 35.6 ± 3.1 years; 72.9% were female, and 61.0% had education at a bachelor degree or higher (Table 1).

The primary endpoint was achieved by 42.9% and 27.6% of the parents in the SIDCER ICF group and the conventional ICF group, respectively (RR = 1.552, 95%CI = 1.061 to 2.270, p = 0.021). The parents in the SIDCER ICF group obtained higher total scores when compared to the conventional ICF group (total score: 18.07 ± 3.71 *vs*. 15.98 ± 4.56, mean difference = 2.09, 95% CI = 0.96 to 3.22, p = <0.001). After adjustment for age, gender, and education, a significant difference in the total score between the two groups was still evident (B = 2.75, SE = 0.54, beta = 0.32, 95% CI = 1.69 to 3.81, p <0.001). The values of other secondary endpoints are presented in Table 2.

Proportions of the parents who correctly answered each element of the ICF content were compared between the two groups. The SIDCER ICF was found to be superior to the conventional ICF in improving parental understanding on five elements: who can access the data, right to receive new information, identification of experimental procedures, alternative course of treatment, and number of subjects required (Table 3). The element that was least

understood by the parents in both groups was trial treatment and random assignment; only 66 (out of 210) parents (31.4%) answered this element correctly.

Discussion

This is the first randomized-controlled study which was designed to test the applicability and effectiveness of the SIDCER ICF methodology in a setting of pediatric drug trial. The SIDCER ICF was found to be superior to the conventional ICF in improving parental understanding of several elements of the ICF content. The overall results of this study are consistent with three previous informed consent studies that exhibited the improvement of participants' understanding by the SIDCER ICF.[17,19,20] In line with a recent integrative review on informed consent, it is reasonable to assume that the evidence of improved participants' understanding by the SIDCER ICF is largely attributable to its simplicity and concise format with increased processability (using summary boxes, highlights, and illustrations, when appropriate).[23]

Close examination of the data revealed that the SIDCER ICF was superior to the conventional ICF in improving the parental understanding of trial information in five elements: who can access the data, right to receive new information, identification of experimental procedures, alternative course of treatment, and number of subjects required. The first three elements were highlighted and made salient in the SIDCER ICF, whereas the same content was ordinarily described in the conventional ICF. It is reasonable to assume that a higher understanding of these three elements in the SIDCER ICF group was partly attributed to a complementary technique being used to convey key information. This might be the evidence

to support that increased processability of key or complex information in an ICF could contribute to a significant improvement in parental understanding of such information.[23]

The element that was least understood by the parents in both groups was trial treatment and random assignment. This finding supports lines of the evidence demonstrating that there is the apparent universality of a limited understanding on the aspect of random allocation of the intervention in clinical trials.[24-25] Despite an attempt with increased processability in the SIDCER ICF to aid in description on the concept of randomization (using illustrations and highlights), a large proportion of the parents (63.8%) still did not understand it accurately. This emphasizes the need of increased attention in particular during informed consent discussion to ensure adequate understanding of this concept among individuals who consent to a trial.[26] A combination of the SIDCER ICF methodology with other means (*e.g.*, an integrated cognitive approach[27]) may enhance parental understanding of this information in pediatric research.

Although the overall results demonstrated that the SIDCER ICF was proven superior to the conventional ICF, the degree of parental understanding remained unsatisfactory. Deficiencies in understanding were still prevalent even among those who read the SIDCER ICF. Continued consideration of the normative and practical aspects of informed consent is needed in an attempt to facilitate understanding among parents who act as proxies for their child's participation in research.[28,29] It may be worthwhile to consider using more graphics or pictographs to enhance visualization of complex information in the SIDCER ICF,[30] and further

research may be required to determine the effectiveness of such additional means, especially in this group of population. In addition to the enhanced ICF, a dialogue between the investigator (or a person designated by the investigator) and the parents are still indispensable, while complimentary methods of delivering trial-related information (*e.g.*, a multimedia video and website[27]) may be warranted in some studies. Furthermore, formal evaluation of parental understanding during the process of informed consent may be necessary, especially in pediatric research that poses relatively high risks, with little or no potential direct benefit, to child subjects.[31,32] Accordingly, any inaccuracy of parental understanding could be rectified to ascertain the validity of parental consent obtained in such research.

Of note, this study was confined to parental understanding of an ICF while the child's understanding of an assent form was not studied. It is also possible that the SIDCER ICF methodology may be modified and used to improve the quality of assent forms for pediatric populations. As such, further ICF studies involving pediatric populations are warranted.

In conclusion, the present study demonstrated that the SIDCER ICF methodology was applicable to pediatric research requiring parental consent and effective in improving parental understanding of trial information. However, deficiencies in understanding were still prevalent among the parents of child subjects, at least, in this setting, suggesting that further research is required to improve parental understanding in pediatric research.

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Contributor: The study was designed by Nut Koonrungsesomboon and Juntra Karbwang, and conducted by Chanchai Traivaree and Charnunnut Tiyapsane. Data analysis was done by Nut Koonrungsesomboon. The manuscript was written by Nut Koonrungsesomboon and revised by Juntra Karbwang, with contributions from all authors. All authors approved the final version submitted.

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Competing interests: We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

Ethics approval: This study was approved by the Institutional Review Board of Royal Thai

Army Medical Department (No. IRB/RTA1200/2557). Informed consent was obtained by action.

Data sharing statement: Deidentified participant data will be available upon reasonable request by contacting the corresponding author.

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336 2015;41:521-528.

Table 1 Demographic data of the parents (n = 210)

	SIDCER ICF (n = 105)	**Conventional ICF** (n = 105)
Gender (n)		
Male	30 (28.6%)	27 (25.7%)
Female	75 (71.4%)	78 (74.3%)
Age (year)	33.9 ± 12.7	37.4 ± 13.3
Education (n)		
High school or below	49 (46.7%)	33 (31.4%)
Bachelor degree or above	56 (53.3%)	72 (68.6%)

Data represent the number (percentage) of parents or mean ± SD.

Table 2 Comparisons of the total score, the score in each category of the ICF content, and time spent between the two groups

	SIDCER ICF (n = 105)	**Conventional ICF** (n = 105)	**Mean difference**	**95% CI**	**p value***	**Effect size****
Total score (out of 24)	18.07 ± 3.71	15.98 ± 4.56	2.09	(0.96 to 3.22)	<0.001	0.49
Score in the general items (out of 5)	3.99 ± 1.05	3.71 ± 1.16	0.28	(-0.03 to 0.58)	0.072	0.25
Score in the patient's rights (out of 4)	3.41 ± 0.83	3.23 ± 1.07	0.18	(-0.08 to 0.44)	0.172	0.19
Score in the scientific aspects (out of 8)	5.51 ± 1.70	4.50 ± 1.80	1.02	(0.54 to 1.50)	<0.001	0.56
Score in the ethics aspects (out of 7)	5.15 ± 1.52	4.54 ± 1.74	0.61	(0.17 to 1.05)	0.007	0.37
Time spent reading a given ICF (minutes)	23.61 ± 12.51	30.90 ± 15.45	-7.30	(-11.12 to -3.47)	<0.001	0.50
Time spent completing the questionnaire (minutes)	24.48 ± 12.84	30.59 ± 13.29	-6.11	(-9.67 to -2.56)	0.001	0.46

Data represent mean ± SD. *Student t-test. **Cohen's d value.

Table 3 Comparisons of the parental understanding of each element of the ICF content between the two groups

	SIDCER ICF (n = 105)		Conventional ICF (n = 105)		Relative Risk (95%CI)		p value*
General items							
1. Recognition that this is research	80	(76.2%)	78	(74.3%)	1.026	(0.878-1.198)	0.749
2. Subjects' responsibility	85	(81.0%)	84	(80.0%)	1.012	(0.886-1.156)	0.862
3. Confidentiality of records	74	(70.5%)	64	(61.0%)	1.156	(0.950-1.408)	0.146
4. Who can access the data	82	(78.1%)	68	(64.8%)	1.206	(1.014-1.435)	0.032
5. Research contact persons	98	(93.3%)	96	(91.4%)	1.021	(0.944-1.103)	0.603
Patient's rights							
6. Right to refuse	76	(72.4%)	87	(82.9%)	0.874	(0.754-1.012)	0.069
7. Right to withdraw	95	(90.5%)	87	(82.9%)	1.092	(0.981-1.215)	0.104
8. Consequences of withdrawal	96	(91.4%)	87	(82.9%)	1.103	(0.994-1.225)	0.064
9. Right to receive new information	91	(86.7%)	78	(74.3%)	1.167	(1.019-1.336)	0.024
Scientific aspects							
10. Eligibility of the subject	81	(77.1%)	72	(68.6%)	1.125	(0.953-1.328)	0.163
11. Number of subjects required	87	(82.9%)	43	(41.0%)	2.023	(1.583-2.587)	<0.001
12. Purpose of the study	80	(76.2%)	75	(71.4%)	1.067	(0.908-1.254)	0.433
13. Trial treatment and random assignment	38	(36.2%)	28	(26.7%)	1.357	(0.904-2.038)	0.137
14. Trial procedures	65	(61.9%)	52	(49.5%)	1.250	(0.979-1.596)	0.071
15. Identification of experimental procedures	80	(76.2%)	66	(62.9%)	1.212	(1.011-1.454)	0.036
16. Duration of the subject's participation	88	(83.8%)	79	(75.2%)	1.114	(0.970-1.279)	0.124
17. Storage and reuse of human materials	60	(57.1%)	57	(54.3%)	1.053	(0.827-1.340)	0.677
Ethics aspects							
18. Alternative course of treatment	94	(89.5%)	82	(78.1%)	1.146	(1.016-1.293)	0.025
19. Foreseeable risks	70	(66.7%)	61	(58.1%)	1.148	(0.929-1.418)	0.200
20. Expected direct/indirect benefits	52	(49.5%)	42	(40.0%)	1.238	(0.914-1.677)	0.165
21. Post-trial benefits	82	(78.1%)	72	(68.6%)	1.139	(0.966-1.342)	0.119
22. Prorated payment for participation	91	(86.7%)	84	(80.0%)	1.083	(0.959-1.223)	0.195
23. Anticipated expenses	60	(57.1%)	53	(50.5%)	1.132	(0.880-1.456)	0.333
24. Compensation for injury	92	(87.6%)	83	(79.0%)	1.108	(0.981-1.252)	0.096

Data represent the number (percentage) of parents. *χ^2 test.

Figure legends

Fig. 1 Flow diagram of this ICF study

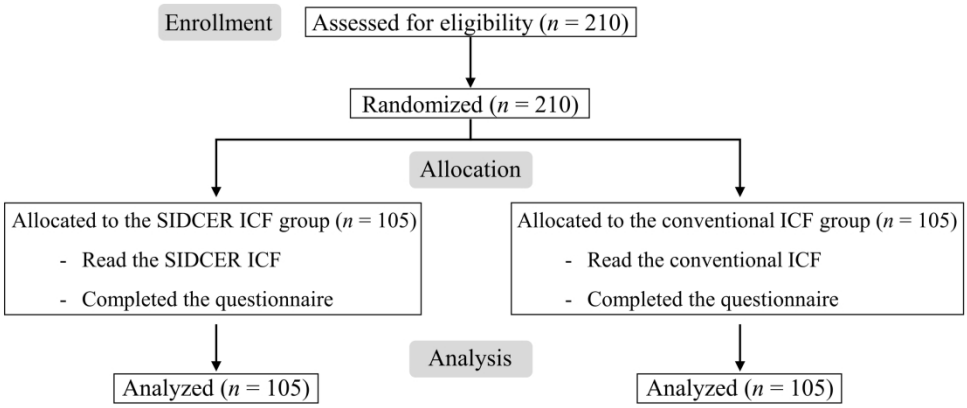

Fig. 1 Flow diagram of this ICF study

227x98mm (300 x 300 DPI)

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3-4
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	6-7
	2b	Specific objectives or hypotheses	7
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	8
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	n/a
Participants	4a	Eligibility criteria for participants	8
	4b	Settings and locations where the data were collected	8
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	9
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	9-10
	6b	Any changes to trial outcomes after the trial commenced, with reasons	n/a
Sample size	7a	How sample size was determined	8-9
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n/a
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	10
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	10
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	10
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	10

Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	n/a
	11b	If relevant, description of the similarity of interventions	n/a
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	11
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	11
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	12
	13b	For each group, losses and exclusions after randomisation, together with reasons	n/a
Recruitment	14a	Dates defining the periods of recruitment and follow-up	12
	14b	Why the trial ended or was stopped	n/a
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Fig. 1
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	12-13, Tables 2
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	12-13
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	12-13, Table 3
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	n/a
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	14-16
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	14-16
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	14-16
Other information			
Registration	23	Registration number and name of trial registry	n/a
Protocol	24	Where the full trial protocol can be accessed, if available	n/a
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	17

n/a, not applicable

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Improved parental understanding by an enhanced informed consent form: a randomized controlled study nested in a pediatric drug trial

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TITLE PAGE

Title: Improved parental understanding by an enhanced informed consent form: a randomized controlled study nested in a pediatric drug trial

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Key words: Informed consent; Parental consent; Pediatrics; Consent forms; Comprehension.

Abstract

Objective: This study was designed to evaluate the applicability and effectiveness of the enhanced informed consent form (ICF) methodology, proposed by the Strategic Initiative for Developing Capacity in Ethical Review (SIDCER), in pediatric research requiring parental consent. The objective of this study was to compare the parental understanding of information between the parents who read the SIDCER ICF and those who read the conventional ICF.

Design: A prospective, randomized-controlled design.

Setting: Pediatric Outpatients Department, Phramongkutklao Hospital, Thailand.

Participants: 210 parents of children with thalassemia (age = 35.6 ± 13.1 years).

Interventions: The parents were randomly assigned to read either the SIDCER ICF (n = 105) or the conventional ICF (n = 105) of a pediatric drug trial.

Primary and secondary outcome measures: Parental understanding of trial information was determined using 24 scenario-based questions. The primary endpoint was the proportion of parents who obtained the understanding score of more than 80%, and the secondary endpoint was the total score.

Results: Forty-five parents (42.9%) in the SIDCER ICF group and 29 parents (27.6%) in the conventional ICF group achieved the primary endpoint (relative risk = 1.552, 95%CI = 1.061 to 2.270, p = 0.021). The total score of the parents in the SIDCER ICF group was significantly higher than the conventional ICF group (18.07 ± 3.71 *vs*. 15.98 ± 4.56, p = 0.001).

Conclusions: The SIDCER ICF was found to be superior to the conventional ICF in improving parental understanding of trial information.

Strengths and limitations of the study

- This study was a comparative, randomized-controlled study, in which the SIDCER ICF (study intervention) was directly compared to the conventional ICF (control) to establish superiority.
- This study was conducted on actual parents deciding whether or not to allow their child to participate in a pediatric drug trial.
- This study was confined to the parental understanding of an ICF while the child's understanding of an assent form was not studied.
- The findings were largely confined to research contexts in Thailand and may not account for other settings.

Introduction

In pediatric research, enrollment of child subjects generally requires parental permission.[1] Adequate parental understanding of trial information is one of the keys to the ethical conduct of pediatric research because informed parents can act, as proxy decision makers, in their child's best interests and protect their child from assuming unreasonable risks.[2] Despite increasing ethical and regulatory scrutiny, deficiencies still exist in parental understanding; some parents have consented to research without understanding the experimental nature of it and the risks involved, or even that they are consenting on behalf of their child.[3-7]

An informed consent form (ICF) serves as a mandatory document to provide trial relevant information to the participants/surrogate decision makers and document their consent; it consists of the information sheet and the consent certificate. Although the form alone may not be sufficient to achieve a proper, valid consent, it does serve multiple purposes in clinical trials, including the assurance of complete disclosure of information and the enhancement of participants' comprehension.[8] Ideally, an ICF given to parents in pediatric research should be complete, concise, and understandable so that it would enable them to come to an informed decision in regard to their child's participation in a study.[9] In reality, empirical observations reveal a number of lengthy, detailed, and complicated ICFs which are unlikely to be read and understood by general laypersons.[10-12] Most ICF templates still seem to require a high level of

reading comprehension.[13] It has been suggested that the written language in quite a few ICFs stems from a desire to provide legal protection to investigators and sponsors rather than one designed to inform participants/surrogates for rational decision making.[14] At present, there is wide agreement that informed consent (including parental permission) requires more than a signature on a form: efforts should be put to promote understanding of consent information.[15]

The Strategic Initiative for Developing Capacity in Ethical Review (SIDCER) has recently proposed the 'enhanced ICF development' methodology, named 'SIDCER ICF', in response to the need for making an ICF complete, concise and understandable.[16] The SIDCER ICF methodology has been tested in real informed consent settings involving several clinical trials and it has been shown to be effective in improving participants' understanding.[17] As such, it is compelling to extend the application of the SIDCER ICF methodology to clinical research requiring proxy consent. Therefore, the present study was designed to test the applicability and effectiveness of the SIDCER ICF in pediatric research requiring parental consent. The objective of this study was to compare the parental understanding of information between the parents who read the SIDCER ICF and those who read the conventional ICF.

Materials and Methods

This open-label, comparative, randomized-controlled study determined the effectiveness of two different ICFs – the SIDCER ICF and the conventional ICF (1:1) – on parental understanding of research-related information. The study protocol and related documents obtained ethical approval from the Institutional Review Board of Royal Thai Army Medical Department.

Study participants

Parents of children with transfusion-dependent thalassemia were informed about this ICF study and were recruited by study nurse at the Pediatric Outpatients Department, Phramongkutklao Hospital, Bangkok, Thailand. They were invited to read either the SIDCER ICF or the conventional ICF (by random assignment) for possible enrollment of their child (aged 1-18 years) in a drug trial which investigated the effects of furosemide on markers of volume overload in children with transfusion-dependent thalassemia.[18] Informed consent was obtained verbally and by action, that is, answering the questionnaire tacitly inferred their consent for participation in this ICF study.

This ICF study planned to enroll 210 parents (with 105 parents in each arm), based on an *a priori* estimate to detect the hypothesized effect size of 20% difference between two independent proportions of the primary endpoint ($p_1 = 0.8$ and $p_2 = 0.6$), with the precision and confidence level of 95%, 80% power and allocation ratio of 1, with a continuity correction.

This hypothesized effect size was based on the findings in our previous study.[19]

Study interventions

The effectiveness of two different ICF interventions on parental understanding were compared: one was the original, standard ICF of the pediatric drug trial (in Thai) and another was the enhanced (SIDCER) ICF of the trial (in Thai). The former comprising six pages with 2,065 words was considered as the conventional ICF; trial-related information was described using text in standard sequences. The latter comprising four pages with 1,644 words was developed according to the SIDCER ICF methodology, comprehensively described elsewhere.[16] In brief, essential information as is relevant to the parents' decision making was summarized in the SIDCER ICF template (available from http://ijme.in/pdf/appendix-1.pdf?v=1) in a narrative and illustrative manner, according to the SIDCER ICF principles. The drafted SIDCER ICF was, then, reviewed by laypersons to enhance the readability and understandability of written information. Both conventional and SIDCER ICFs contained the same content.

Study outcomes

Parental understanding of essential research-related information was measured using the questionnaire (in Thai), which was modified from our previous studies.[17,19,20] It consisted of 24 scenario-based questions which assessed parental understanding of relevant ICF content in the following categories: general items (five questions), patient's rights (four questions),

scientific aspects (eight questions), and ethics aspects (seven questions). Each question with three possible answers was structured in a way that the parents would have had to apply their understanding of information given in an ICF to the scenario.[21] In each question, there was only one correct answer, counting as a score of 1, making the highest possible score 24. The primary endpoint was the proportion of parents obtaining the total score of more than 80% (≥20/24). The secondary endpoints were the total score, the score of each category, and time spent reading a given ICF and completing the questionnaire.

Study procedure

For allocation of the parents, a computer-generated list of random numbers was applied, and a randomization code was packed in an opaque sealed envelope before subject enrollment to this ICF study. Eligible parents were randomly assigned to read either the SIDCER ICF or the conventional ICF. After that, the questionnaire was distributed. The parents could keep and read the ICF while completing the questionnaire, but they could not ask any questions during this process. Time spent reading the given ICF and completing the questionnaire was recorded and this was the end of the ICF study. The informed consent process continued for the clinical trial for both groups in the same manner, that is, informed consent discussion with the parents was conducted and any inaccurate understanding of trial information was explained prior to the parents' decision whether or not to sign consent for their child's participation in the pediatric drug trial.

Patient and public involvement

The present study did not involve patients or publics during the development of research question and outcome measures as well as in the study design and recruitment plan. Patient burden was not assessed formally, but assumed to be low. Results will be disseminated via this publication, with a lay summary of the results in Thai.

Data analysis

Descriptive statistics were used to describe the basic features of the data in this study. The proportion of the parents in the SIDCER ICF group who achieved the outcome divided by that of the conventional ICF group was presented using the term 'relative risk' (RR). Dichotomous variables were compared using χ^2 test. Continuous variables were presented in mean ± standard deviation (SD), and the values between the two groups were compared using the Student *t*-test. Cohen's *d* was used to classify the effect size as small ($d = 0.2$), medium ($d = 0.5$), and large ($d = 0.8$).[22] Multivariable linear regression analysis was performed to evaluate the relationship between different ICF interventions and the total score after adjusting for age, gender, and education. All statistical analysis was executed using IBM SPSS Statistics for Windows, Version 22.0, with a p value of less than 0.05 considered to indicate statistical significance.

Results

Two hundred and ten parents of thalassemia children were enrolled between September 2015 and September 2016 and equally assigned to the SIDCER ICF group (n = 105) and the conventional ICF group (n = 105) (Fig. 1). The mean age of 210 enrolled parents was 35.6 ± 3.1 years; 72.9% were female, and 61.0% had education at a bachelor degree or higher (Table 1).

The primary endpoint was achieved by 42.9% and 27.6% of the parents in the SIDCER ICF group and the conventional ICF group, respectively (RR = 1.552, 95%CI = 1.061 to 2.270, p = 0.021). The parents in the SIDCER ICF group obtained higher total scores when compared to the conventional ICF group (total score: 18.07 ± 3.71 *vs*. 15.98 ± 4.56, mean difference = 2.09, 95% CI = 0.96 to 3.22, p = <0.001). After adjustment for age, gender, and education, a significant difference in the total score between the two groups was still evident (B = 2.75, SE = 0.54, beta = 0.32, 95% CI = 1.69 to 3.81, p <0.001). The values of other secondary endpoints are presented in Table 2.

Proportions of the parents who correctly answered each element of the ICF content were compared between the two groups. The SIDCER ICF was found to be superior to the conventional ICF in improving parental understanding on five elements: who can access the data, right to receive new information, identification of experimental procedures, alternative course of treatment, and number of subjects required (Table 3). The element that was least

understood by the parents in both groups was trial treatment and random assignment; only 66 (out of 210) parents (31.4%) answered this element correctly.

Discussion

This is the first randomized-controlled study which was designed to test the applicability and effectiveness of the SIDCER ICF methodology in a setting of pediatric drug trials. The SIDCER ICF was found to be superior to the conventional ICF in improving parental understanding of several elements of the ICF content. The overall results of this study are consistent with three previous informed consent studies that exhibited the improvement of participants' understanding by the SIDCER ICF.[17,19,20] In line with a recent integrative review on informed consent, it is reasonable to assume that the evidence of improved participants' understanding by the SIDCER ICF is largely attributable to its simplicity and concise format with increased processability (using summary boxes, highlights, and illustrations, when appropriate).[23]

Close examination of the data revealed that the SIDCER ICF was superior to the conventional ICF in improving the parental understanding of trial information in five elements: who can access the data, right to receive new information, identification of experimental procedures, alternative course of treatment, and number of subjects required. The first three elements were highlighted and made salient in the SIDCER ICF, whereas the same content was ordinarily described in the conventional ICF. It is reasonable to assume that a higher understanding of these three elements in the SIDCER ICF group was partly attributed to a complementary technique being used to convey key information. This might be the evidence

to support that increased processability of key or complex information in an ICF could contribute to a significant improvement in parental understanding of such information.[23]

The element that was least understood by the parents in both groups was trial treatment and random assignment. This finding supports lines of the evidence demonstrating that there is the apparent universality of a limited understanding on the aspect of random allocation of the intervention in clinical trials.[24-25] Despite an attempt with increased processability in the SIDCER ICF to aid in description on the concept of randomization (using illustrations and highlights), a large proportion of the parents (63.8%) still did not understand it accurately. This emphasizes the need of increased attention in particular during informed consent discussion to ensure adequate understanding of this concept among individuals who consent to a trial.[26] A combination of the SIDCER ICF methodology with other means (*e.g.*, an integrated cognitive approach) may enhance parental understanding of this information in pediatric research.[27]

Although the overall results suggested that the SIDCER ICF was superior to the conventional ICF in this setting, the degree of parental understanding remained unsatisfactory. Deficiencies in understanding were still prevalent even among those who read the SIDCER ICF. Moreover, we have noticed that the level of parental understanding in this study is apparently lower than our observations in the previous ICF studies involving other groups of populations.[17,19,20] Continued consideration of the normative and practical aspects of informed consent is needed in an attempt to facilitate understanding among parents who act as proxies

for their child's participation in research.[28,29] It may be worthwhile to consider using more graphics or pictographs to enhance visualization of complex information in the SIDCER ICF,[30] and further research may be required to determine the effectiveness of such additional means, especially in this group of populations. In addition to the enhanced ICF, a dialogue between the investigator (or a person designated by the investigator) and the parents are still indispensable, while complimentary methods of delivering trial-related information (*e.g.*, a multimedia video and website[27]) may be warranted in some studies. Furthermore, formal evaluation of parental understanding during the process of informed consent may be necessary, especially in pediatric research that poses relatively high risks, with little or no potential direct benefit, to child subjects.[31,32] Accordingly, any inaccuracy of parental understanding could be rectified to ascertain the validity of parental consent obtained in such research.

Of note, this study was confined to parental understanding of an ICF while the child's understanding of an assent form was not studied. It is also possible that the SIDCER ICF methodology may be modified and used to improve the quality of assent forms for pediatric populations. As such, further ICF studies involving pediatric populations are warranted.

In conclusion, the present study demonstrated that the SIDCER ICF methodology was applicable to pediatric research requiring parental consent and effective in improving parental understanding of trial information. However, deficiencies in understanding were still prevalent among the parents of child subjects, at least, in this setting, suggesting that further research is

required to improve parental understanding in pediatric research.

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Contributor: The study was designed by Nut Koonrungsesomboon and Juntra Karbwang, and conducted by Chanchai Traivaree and Charnunnut Tiyapsane. Data analysis was done by Nut Koonrungsesomboon. The manuscript was written by Nut Koonrungsesomboon and revised by Juntra Karbwang, with contributions from all authors. All authors approved the final version submitted.

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Competing interests: We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

Ethics approval: This study was approved by the Institutional Review Board of Royal Thai

Army Medical Department (No. IRB/RTA1200/2557). Informed consent was obtained by action.

Data sharing statement: Deidentified participant data will be available upon reasonable request by contacting the corresponding author.

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Table 1 Demographic data of the parents (n = 210)

	SIDCER ICF (n = 105)	Conventional ICF (n = 105)
Gender (n)		
Male	30 (28.6%)	27 (25.7%)
Female	75 (71.4%)	78 (74.3%)
Age (year)	33.9 ± 12.7	37.4 ± 13.3
Education (n)		
High school or below	49 (46.7%)	33 (31.4%)
Bachelor degree or above	56 (53.3%)	72 (68.6%)

Data represent the number (percentage) of parents or mean ± SD.

Table 2 Comparisons of the total score, the score in each category of the ICF content, and time spent between the two groups

	SIDCER ICF (n = 105)	**Conventional ICF** (n = 105)	**Mean difference**	**95% CI**	**p value***	**Effect size****
Total score (out of 24)	18.07 ± 3.71	15.98 ± 4.56	2.09	(0.96 to 3.22)	<0.001	0.49
Score in the general items (out of 5)	3.99 ± 1.05	3.71 ± 1.16	0.28	(-0.03 to 0.58)	0.072	0.25
Score in the patient's rights (out of 4)	3.41 ± 0.83	3.23 ± 1.07	0.18	(-0.08 to 0.44)	0.172	0.19
Score in the scientific aspects (out of 8)	5.51 ± 1.70	4.50 ± 1.80	1.02	(0.54 to 1.50)	<0.001	0.56
Score in the ethics aspects (out of 7)	5.15 ± 1.52	4.54 ± 1.74	0.61	(0.17 to 1.05)	0.007	0.37
Time spent reading a given ICF (minutes)	23.61 ± 12.51	30.90 ± 15.45	-7.30	(-11.12 to -3.47)	<0.001	0.50
Time spent completing the questionnaire (minutes)	24.48 ± 12.84	30.59 ± 13.29	-6.11	(-9.67 to -2.56)	0.001	0.46

Data represent mean ± SD. *Student t-test. **Cohen's d value.

Table 3 Comparisons of the parental understanding of each element of the ICF content between the two groups

	SIDCER ICF (n = 105)		Conventional ICF (n = 105)		Relative Risk (95%CI)		p value*
General items							
1. Recognition that this is research	80	(76.2%)	78	(74.3%)	1.026	(0.878-1.198)	0.749
2. Subjects' responsibility	85	(81.0%)	84	(80.0%)	1.012	(0.886-1.156)	0.862
3. Confidentiality of records	74	(70.5%)	64	(61.0%)	1.156	(0.950-1.408)	0.146
4. Who can access the data	82	(78.1%)	68	(64.8%)	1.206	(1.014-1.435)	0.032
5. Research contact persons	98	(93.3%)	96	(91.4%)	1.021	(0.944-1.103)	0.603
Patient's rights							
6. Right to refuse	76	(72.4%)	87	(82.9%)	0.874	(0.754-1.012)	0.069
7. Right to withdraw	95	(90.5%)	87	(82.9%)	1.092	(0.981-1.215)	0.104
8. Consequences of withdrawal	96	(91.4%)	87	(82.9%)	1.103	(0.994-1.225)	0.064
9. Right to receive new information	91	(86.7%)	78	(74.3%)	1.167	(1.019-1.336)	0.024
Scientific aspects							
10. Eligibility of the subject	81	(77.1%)	72	(68.6%)	1.125	(0.953-1.328)	0.163
11. Number of subjects required	87	(82.9%)	43	(41.0%)	2.023	(1.583-2.587)	<0.001
12. Purpose of the study	80	(76.2%)	75	(71.4%)	1.067	(0.908-1.254)	0.433
13. Trial treatment and random assignment	38	(36.2%)	28	(26.7%)	1.357	(0.904-2.038)	0.137
14. Trial procedures	65	(61.9%)	52	(49.5%)	1.250	(0.979-1.596)	0.071
15. Identification of experimental procedures	80	(76.2%)	66	(62.9%)	1.212	(1.011-1.454)	0.036
16. Duration of the subject's participation	88	(83.8%)	79	(75.2%)	1.114	(0.970-1.279)	0.124
17. Storage and reuse of human materials	60	(57.1%)	57	(54.3%)	1.053	(0.827-1.340)	0.677
Ethics aspects							
18. Alternative course of treatment	94	(89.5%)	82	(78.1%)	1.146	(1.016-1.293)	0.025
19. Foreseeable risks	70	(66.7%)	61	(58.1%)	1.148	(0.929-1.418)	0.200
20. Expected direct/indirect benefits	52	(49.5%)	42	(40.0%)	1.238	(0.914-1.677)	0.165
21. Post-trial benefits	82	(78.1%)	72	(68.6%)	1.139	(0.966-1.342)	0.119
22. Prorated payment for participation	91	(86.7%)	84	(80.0%)	1.083	(0.959-1.223)	0.195
23. Anticipated expenses	60	(57.1%)	53	(50.5%)	1.132	(0.880-1.456)	0.333
24. Compensation for injury	92	(87.6%)	83	(79.0%)	1.108	(0.981-1.252)	0.096

Data represent the number (percentage) of parents. *χ^2 test.

Figure legends

Fig. 1 Flow diagram of this ICF study

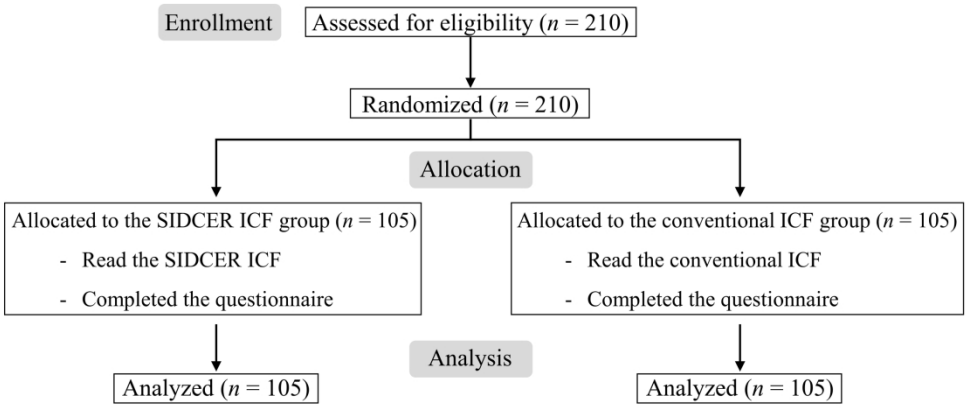

Fig. 1 Flow diagram of this ICF study

227x98mm (300 x 300 DPI)

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3-4
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	6-7
	2b	Specific objectives or hypotheses	7
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	8
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	n/a
Participants	4a	Eligibility criteria for participants	8
	4b	Settings and locations where the data were collected	8
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	9
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	9-10
	6b	Any changes to trial outcomes after the trial commenced, with reasons	n/a
Sample size	7a	How sample size was determined	8-9
	7b	When applicable, explanation of any interim analyses and stopping guidelines	n/a
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	10
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	10
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	10
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	10

Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	n/a
	11b	If relevant, description of the similarity of interventions	n/a
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	11
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	11
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	12
	13b	For each group, losses and exclusions after randomisation, together with reasons	n/a
Recruitment	14a	Dates defining the periods of recruitment and follow-up	12
	14b	Why the trial ended or was stopped	n/a
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Fig. 1
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	12-13, Tables 2
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	12-13
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	12-13, Table 3
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	n/a
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	14-16
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	14-16
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	14-16
Other information			
Registration	23	Registration number and name of trial registry	n/a
Protocol	24	Where the full trial protocol can be accessed, if available	n/a
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	17

n/a, not applicable