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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

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

Author names and affiliations: Nut Koonrunsesomboon¹, Chanchai Traivaree², Charnunnut Tiypsane², Juntra Karbwang³

¹Department of Pharmacology, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand.

²Department of Pediatrics, Phramongkutklo Hospital and Phramongkutklo College of Medicine, Bangkok, Thailand.

³Department of Clinical Product Development, Institute of Tropical Medicine, Nagasaki University, Nagasaki, Japan.

Corresponding author: Juntra Karbwang, M.D., Ph.D., Department of Clinical Product Development, Institute of Tropical Medicine, Nagasaki University, 1-12-4 Sakamoto, Nagasaki 852-8523, Japan, Tel: +81-95-819-7558, Fax: +81-95-819-7846, Email address: karbwangj@nagasaki-u.ac.jp or jkarbwang@yahoo.com

Email address: Nut Koonrunsesomboon: nkoonrung@gmail.com; Chanchai Traivaree: ctrivaree@yahoo.com; Charnunnut Tiypsane: charnunnut332@gmail.com; Juntra Karbwang: jkarbwang@yahoo.com

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

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4 **20 Abstract**
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7 *Objective:* This study aimed to evaluate the applicability and effectiveness of the enhanced
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10 *informed consent form (ICF) methodology, proposed by the Strategic Initiative for Developing*
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13 *Capacity in Ethical Review (SIDCER), in pediatric research requiring parental consent.*
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16 *Design:* A prospective, randomized-controlled design.
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19 *Setting:* Pediatric Outpatients Department, Phramongkutklo Hospital, Thailand.
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22 *Participants:* 210 parents of children with thalassemia.
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25 *Interventions:* The participants were randomly assigned to read either the SIDCER ICF ($n =$
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28 105) or the conventional ICF ($n = 105$) of a pediatric drug trial.
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30 *Primary and secondary outcome measures:* Parental understanding of trial information was
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34 determined using 24 scenario-based questions. The primary endpoint was the proportion of
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37 parents who obtained the understanding score of more than 80%, and the secondary endpoint
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40 was the total score.
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43 *Results:* Forty-five parents (42.9%) in the SIDCER ICF group and 29 parents (27.6%) in the
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45
46 conventional ICF group achieved the primary endpoint (relative risk = 1.552, 95%CI = 1.061
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49 to 2.270, $p = 0.021$). The median total scores of the parents in the SIDCER ICF group and in
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52 the conventional ICF group were 19/24 and 17/24, respectively ($p = 0.001$).
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37 *Conclusions:* The SIDCER ICF was found to be superior to the conventional ICF in improving
38 parental understanding of several elements of the ICF content. Further improvement on the ICF
39 for this group of population is required as deficiencies in understanding were still prevalent.

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4 **40 Strengths and limitations of the study**
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- 7 41 • This randomized-controlled study provides evidence that an informed consent form
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10 42 (ICF) for parental consent of pediatric research could be improved, using the SIDCER
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13 43 ICF methodology.
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16 44 • This study was confined to parental understanding of ICFs while children's
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19 45 understanding of an assent form was not studied.
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22 46 • The findings were largely confined to research contexts in Thailand and may not
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25 47 account for other settings.
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48 **Introduction**

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

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

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4 67 still seem to require a high level of reading comprehension.¹³ The written language in quite a
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7 68 few ICFs stems from a desire to provide legal protection to investigators and sponsors rather
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10 69 than one designed to inform participants/surrogates for rational decision making.¹⁴ At present,
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13 70 there is wide agreement that informed consent (including parental permission) requires more
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16 71 than a signature on a form: efforts should be put to promote understanding of consent
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19 72 information.¹⁵

22 73 The Strategic Initiative for Developing Capacity in Ethical Review (SIDCER) has
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25 74 recently proposed the ‘enhanced ICF development’ methodology, named ‘SIDCER ICF’, in
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28 75 response to the need for making an ICF complete, concise and understandable.¹⁶ The SIDCER
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31 76 ICF methodology has been tested in real informed consent settings involving several clinical
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34 77 trials and it has been shown to be effective in improving participants’ understanding.¹⁷ It is
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37 78 compelling to extend the application of the SIDCER ICF methodology to clinical research
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40 79 requiring proxy consent. The present study was, thus, designed to test the applicability and
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43 80 effectiveness of the SIDCER ICF in pediatric research requiring parental consent.
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81 **Materials and Methods**

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

86 *Study participants*

87 Parents of children with transfusion-dependent thalassemia were recruited at the
88 Pediatric Outpatients Department, Phramongkutklo Hospital, Bangkok, Thailand. They
89 were invited to read either the SIDCER ICF or the conventional ICF (by random assignment)
90 for possible enrollment of their child in a drug trial¹⁸; any refusal to read an ICF given was
91 respected. This ICF study planned to enroll 210 parents (with 105 parents in each arm), based
92 on an *a priori* estimate to detect the hypothesized effect size of 20% difference between two
93 independent proportions of the primary endpoint ($p_1 = 0.8$ and $p_2 = 0.6$), with the precision and
94 confidence level of 95%, 80% power and allocation ratio of 1, with a continuity correction.

95 *Study interventions*

96 The effectiveness of two different ICF interventions on parental understanding were
97 compared: one was the original, standard ICF of the pediatric drug trial (in Thai) and another
98 was the enhanced (SIDCER) ICF of the trial (in Thai). The former comprising six pages with
99 2,065 words was considered as the conventional ICF; trial-related information was described

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4 100 using text in standard sequences. The latter comprising four pages with 1,644 words was
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7 101 developed according to the SIDCER ICF principles and template, comprehensively described
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10 102 elsewhere.¹⁵ The SIDCER ICF contained complete and concise information of the drug trial in
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13 103 an enhanced format using summary boxes, highlights, and illustrations, when appropriate.

16 104 *Study outcomes*

19 105 Parental understanding of essential research-related information was measured using
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22 106 the questionnaire (in Thai). It consisted of 24 scenario-based questions, aimed at assessing
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25 107 parental understanding of 24 required elements of the ICF content: five elements on general
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28 108 aspects, four elements on right aspects, eight elements on scientific aspects, and seven elements
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31 109 on ethical aspects. Of three possible answers in each question, there was only one correct
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34 110 answer, counting as a score of 1, making the total score 24. The primary endpoint was the
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37 111 proportion of parents obtaining the total score of more than 80% ($\geq 20/24$). The secondary
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40 112 endpoints were the total score, the score of each categorical aspect, and time spent reading a
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43 113 given ICF and completing the questionnaire.

46 114 *Study procedure*

49 115 Simple randomization was applied, and a randomization code was generated and
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52 116 packed in an opaque sealed envelope before subject enrollment to this ICF study. Eligible
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55 117 parents were randomly assigned to read either the SIDCER ICF or the conventional ICF. After
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58 118 that, the questionnaire was distributed. The parents could keep and read the ICF while
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4 119 completing the questionnaire, but they could not ask any questions during this process. Time
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7 120 spent reading the given ICF and completing the questionnaire was recorded and this was the
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10 121 end of the ICF study. The informed consent process continued for the clinical trial for both
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13 122 groups in the same manner, that is, informed consent discussion with the parents was conducted
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16 123 and any inaccurate understanding of trial information was explained prior to the parents'
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19 124 decision whether or not to sign consent for their child's participation in a pediatric drug trial.
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22 125 *Data analysis*

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25 126 Descriptive statistics were used to describe the basic features of the data in this study.
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28 127 Dichotomous variables were compared using χ^2 test or Fisher's exact test, as appropriate, and
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31 128 continuous variables were compared using nonparametric statistics (*i.e.*, the Wilcoxon rank-
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34 129 sum test). The proportion of the parents in the SIDCER ICF group who achieved the outcome
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37 130 divided by that of the conventional ICF group was presented using the term 'relative risk (RR)'.
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40 131 Subgroup analysis was done to determine the impact of gender, age and education on the
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43 132 primary endpoint. Multivariable logistic regression analysis was performed to obtain odds ratio
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46 133 (OR), a measure of association between demographic variables and the primary outcome. All
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49 134 statistical analysis was executed using IBM SPSS Statistics for Windows, Version 22.0, with
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52 135 a *p* value of less than 0.05 considered to indicate statistical significance.
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136 **Results**

137 Two hundred and ten parents of thalassemia children were enrolled between
138 September 2015 and September 2016 and equally assigned to the SIDCER ICF group ($n = 105$)
139 and the conventional ICF group ($n = 105$). The mean age of 210 enrolled parents was 35.6
140 (± 3.1) years; 72.9% were female, and 61.0% had education at a bachelor degree or higher
141 (Table 1).

142 The primary endpoint was achieved by 42.9% and 27.6% of the parents in the SIDCER
143 ICF group and the conventional ICF group, respectively (RR = 1.552, 95%CI = 1.061 to 2.270,
144 $p = 0.021$) (Fig. 1). The superiority of the SIDCER ICF over the conventional ICF in improving
145 parental understanding was seen particularly among those aged more than 35 years and those
146 whose education was at a bachelor degree or higher (RR = 1.986, 95%CI = 1.193 to 3.305, $p =$
147 0.006 ; RR = 1.870, 95%CI = 1.234 to 2.834, $p = 0.003$, respectively) (Fig. 1). The multivariable
148 analysis demonstrated that female gender and education at a bachelor degree or higher were
149 independently associated with higher attainment of the primary endpoint (OR = 2.213, 95%CI
150 = 1.067 to 4.591, $p = 0.033$; OR = 2.052, 95%CI = 1.093 to 3.852, $p = 0.025$), whereas age of
151 the parents was not (OR = 1.008, 95%CI = 0.985 to 1.031, $p = 0.485$).

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

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4 155 an ICF: 20 min vs. 30 min, $p < 0.001$). Proportions of the parents who correctly answered each
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7 156 element of the ICF content were compared between the two groups. The SIDCER ICF was
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10 157 found to be superior to the conventional ICF in improving parental understanding on five
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13 158 elements: who can access the data, right to receive new information, identification of
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16 159 experimental procedures, alternative course of treatment, and number of subjects required
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19 160 (Table 3). The element that was least understood by the parents in both groups was trial
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22 161 treatment and random assignment; only 66 (out of 210) parents (31.4%) answered this element
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25 162 correctly.
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163 Discussion

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

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

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4 182 the language used in the ICF must suit the individual's level of understanding. In addition, the
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7 183 present study identified another feature associated with understanding levels of trial
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10 184 information; female parents obtained optimal comprehension of trial information in a higher
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13 185 proportion than male parents did. Although it was unclear to us why female parents did better
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16 186 than male parents, one hypothesis to explain this observation is that women in general might
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19 187 be more information-seeking and tended to read the ICF more thoroughly than men. Female
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22 188 parents might have had more concern about their child's participation in research or might have
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25 189 taken more responsibility of the child's health care than did male parents, so they were more
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28 190 likely to read the ICF and contemplate the information more seriously.²⁴ However, a relatively
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31 191 few male parents in this study might not be a suitable representative of their group.

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34 192 Close examination of the data revealed that the SIDCER ICF was superior to the
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37 193 conventional ICF in increasing the parental understanding of trial information in five elements.
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40 194 First, 'who can access the data'; it is important that the parents should understand the limit of
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43 195 confidentiality of their child's health data, so they would not incorrectly assume their child's
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46 196 health information to be fully kept confidential. This is due to the fact that some authority
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49 197 persons (*e.g.*, the monitors or the regulatory authorities) may be granted direct access to the
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52 198 subject's original medical records as required by regulations. Second, 'right to receive new
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55 199 information'; this element emphasized the nature of informed consent as an ongoing,
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58 200 interactive process. The parents should know that informed consent does not end when they
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4 201 sign the consent form; rather, they would still be kept informed of any new, relevant
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7 202 information that may become available and affect their decision during the course of the trial.
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10 203 Third, ‘identification of experimental procedures’; this element could help parents distinguish
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13 204 the procedures that are experimental in the trial from those used in routine care and recognize
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16 205 that research is not the same as standard care.²⁵ The additional risks derived from experimental
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19 206 procedures should be understood and accepted by the parents before they let their child
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22 207 participate in a trial. Fourth, ‘alternative course of treatment’; this element provided
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25 208 information about other options that the child would have had if his/her parents decided not to
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28 209 let him/her participate in the study. Understanding of this element would ensure the
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31 210 voluntariness of trial participation. The parents should recognize that trial participation is not
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34 211 the only option available for their child. Fifth, ‘number of subjects required’; this element
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37 212 informed parents about the approximate number of children that the trial would recruit. This
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40 213 information could be material to decision making for trial participation in some settings; for
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43 214 example, some parents may be reluctant to let their child participate in a trial involving a small
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46 215 number of children, while they may feel more comfortable when a trial involves a large number
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49 216 of subjects with the same condition as their child.

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52 217 The element that was least understood by the parents in both groups was ‘trial
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55 218 treatment and random assignment’. This finding supports lines of the evidence demonstrating
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58 219 that there is the apparent universality of a limited understanding on the aspect of random
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4 220 allocation of the intervention in clinical trials.²⁶⁻²⁷ Despite an attempt with increased
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7 221 processability in the SIDCER ICF to aid in description on the concept of randomization (using
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10 222 illustrations and highlights), a large proportion of the parents (63.8%) still did not understand
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13 223 it accurately. This emphasizes the need of increased attention in particular during informed
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16 224 consent discussion to ensure adequate understanding of this concept among individuals who
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19 225 consent to a trial.²⁸ A combination of the SIDCER ICF methodology with other means (*e.g.*,
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22 226 an integrated cognitive approach²⁹) may enhance parental understanding of consent
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25 227 information in pediatric research.

28 228 Although the overall results demonstrated that the SIDCER ICF was proven superior
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31 229 to the conventional ICF, the degree of parental understanding remained unsatisfactory.
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34 230 Deficiencies in understanding were still prevalent even among those who read the SIDCER
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37 231 ICF. Truong *et al* observed that parents of children with poor prognoses seem to understand
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40 232 trial information better than do parents of children with more favorable prognoses.³⁰ Continued
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43 233 consideration of the normative and practical aspects of informed consent is needed in an
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46 234 attempt to facilitate understanding among parents who act as proxies for their child's
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49 235 participation in research.^{31,32} It may be worthwhile to consider using more graphics or
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52 236 pictographs to enhance visualization of complex information,³³ and further research may be
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55 237 required to determine the effectiveness of such additional means in this group of population. A
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58 238 dialogue between the investigator (or a person designated by the investigator) and the parents
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4 239 are still indispensable, while complimentary methods of delivering trial-related information
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7 240 (*e.g.*, a multimedia video and website²⁹) may be warranted in some studies. Furthermore,
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10 241 formal evaluation of parental understanding during the process of informed consent may be
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13 242 necessary in pediatric research that poses relatively high risks, with little or no potential direct
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16 243 benefit, to child subjects.^{34,35} Accordingly, any inaccuracy of parental understanding could be
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19 244 rectified to ascertain the validity of parental consent obtained in such research.
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22 245 Of note, this study was confined to parental understanding of ICFs while children's
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25 246 understanding of an assent form was not studied. It is also possible that the SIDCER ICF
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28 247 methodology may be modified and used to improve the quality of assent forms for pediatric
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31 248 populations. As such, further ICF studies involving pediatric populations are warranted.
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34 249 In conclusion, the present study demonstrated that the SIDCER ICF methodology was
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37 250 applicable to pediatric research requiring parental consent and effective in improving parental
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40 251 understanding of trial information. However, deficiencies in understanding were still prevalent
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43 252 among the parents of child subjects, at least, in this setting, suggesting that further research is
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46 253 required to improve parental understanding in pediatric drug trials.
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8
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12
13 257 from laypersons' perspectives.

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17
18
19 259 conducted by Chanchai Traivaree and Charnunnut Tiyapsane. Data analysis was done by Nut
20
21
22 260 Koonrunksesomboon. The manuscript was written by Nut Koonrunksesomboon and revised
23
24
25 261 by Juntra Karbwang, with contributions from all authors. All authors approved the final version
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46 268 interpretation of the data; preparation, review or approval of the manuscript; and decision to
47
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49 269 submit this manuscript for publication.

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52 270 **Competing interests:** We have read and understood BMJ policy on declaration of interests
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55 271 and declare that we have no competing interests.

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58 272 **Ethics approval:** This study was approved by ...
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4 273 **Data sharing statement:** The participants did not give consent for data to be shared beyond
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7 274 the research team.
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357 **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%)

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

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4 **Table 2** The total score, the score in each categorical aspect of the ICF content, and time spent
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7 361 reading a given ICF and completing the questionnaire
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	SIDCER ICF (<i>n</i> = 105)	Conventional ICF (<i>n</i> = 105)	<i>p</i>
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

25 362 Data represent median (interquartile range, Q_1 to Q_3).

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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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366 **Figure legends**

367 **Fig. 1** Proportions of the parents whose understanding score was more than 80% ($\geq 20/24$)

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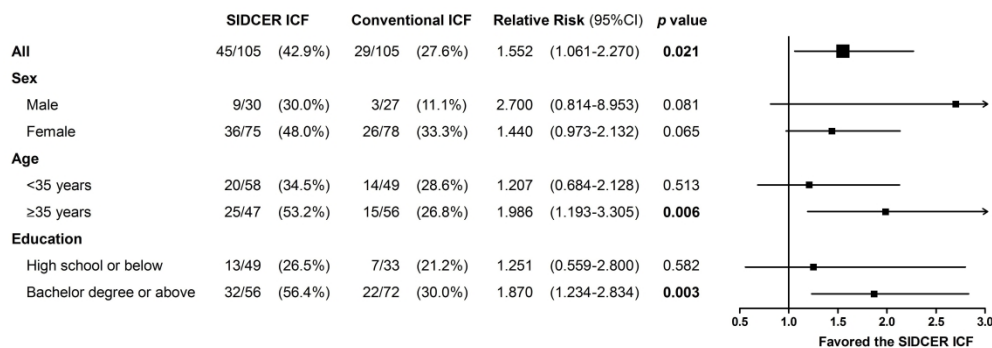


Fig. 1 Proportions of the parents whose understanding score was more than 80% ($\geq 20/24$)



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
	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	8

1	Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	n/a
2				
3		11b	If relevant, description of the similarity of interventions	n/a
4	Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	9
5		12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	9
6				
7	Results			
8	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
9		13b	For each group, losses and exclusions after randomisation, together with reasons	n/a
10	Recruitment	14a	Dates defining the periods of recruitment and follow-up	10
11		14b	Why the trial ended or was stopped	n/a
12	Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
13	Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	10
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15	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
16		17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	10-11, Fig. 1
17	Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	10-11
18				
19	Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	n/a
20				
21	Discussion			
22	Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	12-16
23	Generalisability	21	Generalisability (external validity, applicability) of the trial findings	12-16
24	Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	12-16
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26	Other information			
27	Registration	23	Registration number and name of trial registry	n/a
28	Protocol	24	Where the full trial protocol can be accessed, if available	n/a
29	Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	17

n/a, not applicable

BMJ Open

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

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Secondary Subject Heading:	Paediatrics
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Manuscripts

TITLE PAGE

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

Author names and affiliations: Nut Koonrunsesomboon^{1,2}, Chanchai Traivaree³, Charnunnut Tiyapsane³, Juntra Karbwang⁴

¹Department of Pharmacology, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand.

²Musculoskeletal Science and Translational Research (MSTR), Chiang Mai University, Chiang Mai, Thailand.

³Department of Pediatrics, Phramongkutklo Hospital and Phramongkutklo College of Medicine, Bangkok, Thailand.

⁴Department of Clinical Product Development, Institute of Tropical Medicine, Nagasaki University, Nagasaki, Japan.

Corresponding author: Juntra Karbwang, M.D., Ph.D., Department of Clinical Product Development, Institute of Tropical Medicine, Nagasaki University, 1-12-4 Sakamoto, Nagasaki 852-8523, Japan, Tel: +81-95-819-7558, Fax: +81-95-819-7846, Email address: karbwangj@nagasaki-u.ac.jp or jkarbwang@yahoo.com

Email address: Nut Koonrunsesomboon: nkoonrung@gmail.com; Chanchai Traivaree: ctrivaree@yahoo.com; Charnunnut Tiyapsane: charnunnut332@gmail.com; Juntra Karbwang:

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7 21 **Key words:** Informed consent; Parental consent; Pediatrics; Consent forms; Comprehension.
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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, Phramongkutklo 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 , $p = 0.001$).

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4 41 *Conclusions:* The SIDCER ICF was found to be superior to the conventional ICF in improving
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7 42 parental understanding of trial information.
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4 43 **Strengths and limitations of the study**

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10 45 (study intervention) was directly compared to the conventional ICF (control) to
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13 46 establish superiority.
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16 47 • This study was conducted on actual parents deciding whether or not to allow their child
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19 48 to participate in a pediatric drug trial.
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22 49 • This study was confined to the parental understanding of an ICF while the child's
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25 50 understanding of an assent form was not studied.
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28 51 • The findings were largely confined to research contexts in Thailand and may not
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53 Introduction

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

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

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4 72 reading comprehension.¹³ It has been suggested that the written language in quite a few ICFs
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7 73 stems from a desire to provide legal protection to investigators and sponsors rather than one
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10 74 designed to inform participants/surrogates for rational decision making.¹⁴ At present, there is
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13 75 wide agreement that informed consent (including parental permission) requires more than a
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16 76 signature on a form: efforts should be put to promote understanding of consent information.¹⁵
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19 77 The Strategic Initiative for Developing Capacity in Ethical Review (SIDCER) has
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22 78 recently proposed the ‘enhanced ICF development’ methodology, named ‘SIDCER ICF’, in
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25 79 response to the need for making an ICF complete, concise and understandable.¹⁶ The SIDCER
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28 80 ICF methodology has been tested in real informed consent settings involving several clinical
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31 81 trials and it has been shown to be effective in improving participants’ understanding.¹⁷ As such,
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34 82 it is compelling to extend the application of the SIDCER ICF methodology to clinical research
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37 83 requiring proxy consent. Therefore, the present study was designed to test the applicability and
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40 84 effectiveness of the SIDCER ICF in pediatric research requiring parental consent. The
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43 85 objective of this study was to compare the parental understanding of information between the
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87 **Materials and Methods**

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

93 *Study participants*

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

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

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4 106 This hypothesized effect size was based on the findings in our previous study.¹⁹
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7 107 *Study interventions*
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10 108 The effectiveness of two different ICF interventions on parental understanding were
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13 109 compared: one was the original, standard ICF of the pediatric drug trial (in Thai) and another
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16 110 was the enhanced (SIDCER) ICF of the trial (in Thai). The former comprising six pages with
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19 111 2,065 words was considered as the conventional ICF; trial-related information was described
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22 112 using text in standard sequences. The latter comprising four pages with 1,644 words was
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25 113 developed according to the SIDCER ICF methodology, comprehensively described
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28 114 elsewhere.¹⁶ In brief, essential information as is relevant to the parents' decision making was
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31 115 summarized in the SIDCER ICF template (available from [http://ijme.in/pdf/appendix-](http://ijme.in/pdf/appendix-1.pdf?v=1)
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34 116 [1.pdf?v=1](http://ijme.in/pdf/appendix-1.pdf?v=1)) in a narrative and illustrative manner, according to the SIDCER ICF principles. The
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37 117 drafted SIDCER ICF was, then, reviewed by laypersons to enhance the readability and
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40 118 understandability of written information. Both conventional and SIDCER ICFs contained the
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43 119 same content.
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46 120 *Study outcomes*
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49 121 Parental understanding of essential research-related information was measured using
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52 122 the questionnaire (in Thai), which was modified from our previous studies.^{17,19,20} It consisted
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55 123 of 24 scenario-based questions which assessed parental understanding of relevant ICF content
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58 124 in the following categories: general items (five questions), patient's rights (four questions),
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4 125 scientific aspects (eight questions), and ethics aspects (seven questions). Each question with
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7 126 three possible answers was structured in a way that the parents would have had to apply their
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10 127 understanding of information given in an ICF to the scenario.²¹ In each question, there was
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13 128 only one correct answer, counting as a score of 1, making the total score 24. The primary
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16 129 endpoint was the proportion of parents obtaining the total score of more than 80% ($\geq 20/24$).
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19 130 The secondary endpoints were the total score, the score of each category, and time spent
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22 131 reading a given ICF and completing the questionnaire.

25 132 *Study procedure*

28 133 For allocation of the parents, a computer-generated list of random numbers was
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31 134 applied, and a randomization code was packed in an opaque sealed envelope before subject
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34 135 enrollment to this ICF study. Eligible parents were randomly assigned to read either the
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37 136 SIDCER ICF or the conventional ICF. After that, the questionnaire was distributed. The parents
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40 137 could keep and read the ICF while completing the questionnaire, but they could not ask any
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43 138 questions during this process. Time spent reading the given ICF and completing the
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46 139 questionnaire was recorded and this was the end of the ICF study. The informed consent
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49 140 process continued for the clinical trial for both groups in the same manner, that is, informed
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52 141 consent discussion with the parents was conducted and any inaccurate understanding of trial
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55 142 information was explained prior to the parents' decision whether or not to sign consent for their
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58 143 child's participation in the pediatric drug trial.

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4 144 *Participant and public involvement*
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7 145 The present study did not involve participants or publics during the development of
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10 146 research question and outcome measures as well as in the study design and recruitment plan.
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13 147 Participant burden was not assessed formally, but assumed to be low. Results will be
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16 148 disseminated via this publication, with a lay summary of the results in Thai.

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19 149 *Data analysis*
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22 150 Descriptive statistics were used to describe the basic features of the data in this study.
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25 151 The proportion of the parents in the SIDCER ICF group who achieved the outcome divided by
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28 152 that of the conventional ICF group was presented using the term 'relative risk' (RR).
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31 153 Dichotomous variables were compared using χ^2 test or Fisher's exact test, as appropriate.
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34 154 Continuous variables were presented in mean \pm standard deviation (SD), and the values
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37 155 between the two groups were compared using the Student *t*-test. Cohen's *d* was used to classify
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40 156 the effect size as small ($d = 0.2$), medium ($d = 0.5$), and large ($d = 0.8$).²² Multivariable linear
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43 157 regression analysis was performed to evaluate the relationship between different ICF
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46 158 interventions and the total score after adjusting for age, gender, and education. All statistical
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49 159 analysis was executed using IBM SPSS Statistics for Windows, Version 22.0, with a *p* value
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52 160 of less than 0.05 considered to indicate statistical significance.
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161 **Results**

162 Two hundred and ten parents of thalassemia children were enrolled between
163 September 2015 and September 2016 and equally assigned to the SIDCER ICF group ($n = 105$)
164 and the conventional ICF group ($n = 105$) (Fig. 1). The mean age of 210 enrolled parents was
165 35.6 ± 3.1 years; 72.9% were female, and 61.0% had education at a bachelor degree or higher
166 (Table 1).

167 The primary endpoint was achieved by 42.9% and 27.6% of the parents in the SIDCER
168 ICF group and the conventional ICF group, respectively (RR = 1.552, 95%CI = 1.061 to 2.270,
169 $p = 0.021$). The parents in the SIDCER ICF group obtained higher total scores when compared
170 to the conventional ICF group (total score: 18.07 ± 3.71 vs. 15.98 ± 4.56 , mean difference =
171 2.09 , 95% CI = 0.96 to 3.22, $p < 0.001$). After adjustment for age, gender, and education, a
172 significant difference in the total score between the two groups was still evident (B = 2.75, SE
173 = 0.54, beta = 0.32, 95% CI = 1.69 to 3.81, $p < 0.001$). The values of other secondary endpoints
174 are presented in Table 2.

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

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4 180 understood by the parents in both groups was trial treatment and random assignment; only 66
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7 181 (out of 210) parents (31.4%) answered this element correctly.
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182 Discussion

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

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

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4 201 to support that increased processability of key or complex information in an ICF could
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7 202 contribute to a significant improvement in parental understanding of such information.²³
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10 203 The element that was least understood by the parents in both groups was trial treatment
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13 204 and random assignment. This finding supports lines of the evidence demonstrating that there
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16 205 is the apparent universality of a limited understanding on the aspect of random allocation of
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19 206 the intervention in clinical trials.²⁴⁻²⁵ Despite an attempt with increased processability in the
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22 207 SIDCER ICF to aid in description on the concept of randomization (using illustrations and
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25 208 highlights), a large proportion of the parents (63.8%) still did not understand it accurately. This
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28 209 emphasizes the need of increased attention in particular during informed consent discussion to
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31 210 ensure adequate understanding of this concept among individuals who consent to a trial.²⁶ A
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34 211 combination of the SIDCER ICF methodology with other means (*e.g.*, an integrated cognitive
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37 212 approach²⁷) may enhance parental understanding of this information in pediatric research.
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40 213 Although the overall results demonstrated that the SIDCER ICF was proven superior
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43 214 to the conventional ICF, the degree of parental understanding remained unsatisfactory.
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46 215 Deficiencies in understanding were still prevalent even among those who read the SIDCER
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49 216 ICF. Continued consideration of the normative and practical aspects of informed consent is
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52 217 needed in an attempt to facilitate understanding among parents who act as proxies for their
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55 218 child's participation in research.^{28,29} It may be worthwhile to consider using more graphics or
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58 219 pictographs to enhance visualization of complex information in the SIDCER ICF,³⁰ and further
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4 220 research may be required to determine the effectiveness of such additional means, especially
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7 221 in this group of population. In addition to the enhanced ICF, a dialogue between the investigator
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10 222 (or a person designated by the investigator) and the parents are still indispensable, while
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13 223 complimentary methods of delivering trial-related information (*e.g.*, a multimedia video and
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16 224 website²⁷) may be warranted in some studies. Furthermore, formal evaluation of parental
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19 225 understanding during the process of informed consent may be necessary, especially in pediatric
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22 226 research that poses relatively high risks, with little or no potential direct benefit, to child
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25 227 subjects.^{31,32} Accordingly, any inaccuracy of parental understanding could be rectified to
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28 228 ascertain the validity of parental consent obtained in such research.

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31 229 Of note, this study was confined to parental understanding of an ICF while the child's
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34 230 understanding of an assent form was not studied. It is also possible that the SIDCER ICF
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37 231 methodology may be modified and used to improve the quality of assent forms for pediatric
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40 232 populations. As such, further ICF studies involving pediatric populations are warranted.

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43 233 In conclusion, the present study demonstrated that the SIDCER ICF methodology was
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46 234 applicable to pediatric research requiring parental consent and effective in improving parental
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49 235 understanding of trial information. However, deficiencies in understanding were still prevalent
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52 236 among the parents of child subjects, at least, in this setting, suggesting that further research is
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55 237 required to improve parental understanding in pediatric research.
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8
9
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13 241 from laypersons' perspectives.

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17
18
19 243 conducted by Chanchai Traivaree and Charnunnut Tiyapsane. Data analysis was done by Nut
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22 244 Koonrungsesomboon. The manuscript was written by Nut Koonrungsesomboon and revised
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25 245 by Juntra Karbwang, with contributions from all authors. All authors approved the final version
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46 252 interpretation of the data; preparation, review or approval of the manuscript; and decision to
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49 253 submit this manuscript for publication.

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52 254 **Competing interests:** We have read and understood BMJ policy on declaration of interests
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55 255 and declare that we have no competing interests.

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58 256 **Ethics approval:** This study was approved by the Institutional Review Board of Royal Thai
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4 257 Army Medical Department (No. IRB/RTA1200/2557). Informed consent was obtained by
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7 258 action.

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10 259 **Data sharing statement:** Deidentified participant data will be available upon reasonable
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13 260 request by contacting the corresponding author.
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337 **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%)

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

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340 **Table 2** Comparisons of the total score, the score in each category of the ICF content, and time
 341 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

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

343

344 **Table 3** Comparisons of the parental understanding of each element of the ICF content between
 345 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

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

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347 **Figure legends**

348 **Fig. 1** Flow diagram of this ICF study

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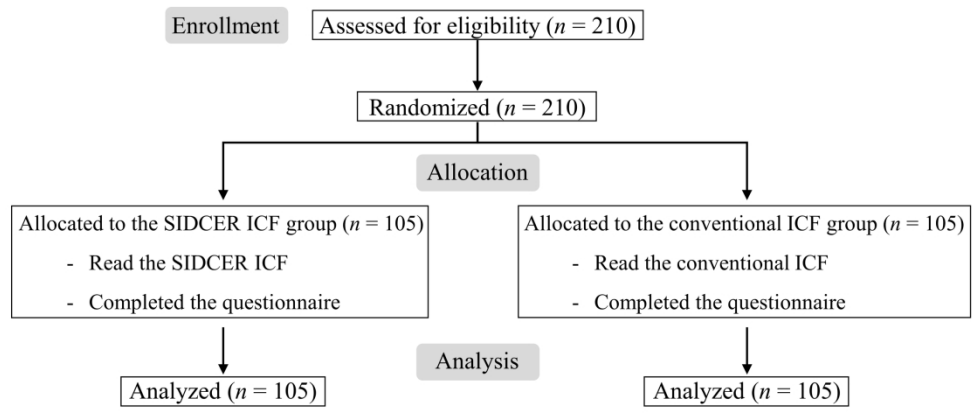


Fig. 1 Flow diagram of this ICF study

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
	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	10

1	Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	n/a
2				
3		11b	If relevant, description of the similarity of interventions	n/a
4	Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	11
5		12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	11
6				
7	Results			
8	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
9		13b	For each group, losses and exclusions after randomisation, together with reasons	n/a
10	Recruitment	14a	Dates defining the periods of recruitment and follow-up	12
11		14b	Why the trial ended or was stopped	n/a
12	Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
13	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
14				
15	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
16		17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	12-13
17	Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	12-13, Table 3
18				
19	Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	n/a
20				
21	Discussion			
22	Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	14-16
23	Generalisability	21	Generalisability (external validity, applicability) of the trial findings	14-16
24	Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	14-16
25				
26	Other information			
27	Registration	23	Registration number and name of trial registry	n/a
28	Protocol	24	Where the full trial protocol can be accessed, if available	n/a
29	Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	17

n/a, not applicable

BMJ Open

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

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Primary Subject Heading:	Ethics
Secondary Subject Heading:	Paediatrics
Keywords:	Informed consent, Parental consent, Consent forms, Pediatrics, Comprehension

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Manuscripts

TITLE PAGE

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

Author names and affiliations: Nut Koonrunsesomboon^{1,2}, Chanchai Traivaree³, Charnunnut Tiyapsane³, Juntra Karbwang⁴

¹Department of Pharmacology, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand.

²Musculoskeletal Science and Translational Research Center, Chiang Mai University, Chiang Mai, Thailand.

³Department of Pediatrics, Phramongkutklo Hospital and Phramongkutklo College of Medicine, Bangkok, Thailand.

⁴Department of Clinical Product Development, Institute of Tropical Medicine, Nagasaki University, Nagasaki, Japan.

Corresponding author: Juntra Karbwang, M.D., Ph.D., Department of Clinical Product Development, Institute of Tropical Medicine, Nagasaki University, 1-12-4 Sakamoto, Nagasaki 852-8523, Japan, Tel: +81-95-819-7558, Fax: +81-95-819-7846, Email address: karbwangj@nagasaki-u.ac.jp or jkarbwang@yahoo.com

Email address: Nut Koonrunsesomboon: nkoonrung@gmail.com; Chanchai Traivaree: ctrivaree@yahoo.com; Charnunnut Tiyapsane: charnunnut332@gmail.com; Juntra Karbwang:

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4 20 jkarbwang@yahoo.com
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7 21 **Key words:** Informed consent; Parental consent; Pediatrics; Consent forms; Comprehension.
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4 **22 Abstract**

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7 *23 Objective:* This study was designed to evaluate the applicability and effectiveness of the
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10 *24 enhanced informed consent form (ICF) methodology, proposed by the Strategic Initiative for*
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13 *25 Developing Capacity in Ethical Review (SIDCER), in pediatric research requiring parental*
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16 *26 consent. The objective of this study was to compare the parental understanding of information*
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19 *27 between the parents who read the SIDCER ICF and those who read the conventional ICF.*

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22 *28 Design:* A prospective, randomized-controlled design.

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25 *29 Setting:* Pediatric Outpatients Department, Phramongkutklo Hospital, Thailand.

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28 *30 Participants:* 210 parents of children with thalassemia (age = 35.6 ± 13.1 years).

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31 *31 Interventions:* The parents were randomly assigned to read either the SIDCER ICF ($n = 105$)
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34 *32 or the conventional ICF ($n = 105$) of a pediatric drug trial.*

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37 *33 Primary and secondary outcome measures:* Parental understanding of trial information was
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40 *34 determined using 24 scenario-based questions. The primary endpoint was the proportion of*
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43 *35 parents who obtained the understanding score of more than 80%, and the secondary endpoint*
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46 *36 was the total score.*

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49 *37 Results:* Forty-five parents (42.9%) in the SIDCER ICF group and 29 parents (27.6%) in the
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52 *38 conventional ICF group achieved the primary endpoint (relative risk = 1.552, 95%CI = 1.061*
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55 *39 to 2.270, $p = 0.021$). The total score of the parents in the SIDCER ICF group was significantly*
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58 *40 higher than the conventional ICF group (18.07 ± 3.71 vs. 15.98 ± 4.56 , $p = 0.001$).*

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4 41 *Conclusions:* The SIDCER ICF was found to be superior to the conventional ICF in improving
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7 42 parental understanding of trial information.
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4 43 **Strengths and limitations of the study**

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7 44 • This study was a comparative, randomized-controlled study, in which the SIDCER ICF
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10 45 (study intervention) was directly compared to the conventional ICF (control) to
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13 46 establish superiority.
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16 47 • This study was conducted on actual parents deciding whether or not to allow their child
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19 48 to participate in a pediatric drug trial.
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22 49 • This study was confined to the parental understanding of an ICF while the child's
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25 50 understanding of an assent form was not studied.
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28 51 • The findings were largely confined to research contexts in Thailand and may not
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31 52 account for other settings.
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53 Introduction

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

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

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4 72 reading comprehension.¹³ It has been suggested that the written language in quite a few ICFs
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7 73 stems from a desire to provide legal protection to investigators and sponsors rather than one
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10 74 designed to inform participants/surrogates for rational decision making.¹⁴ At present, there is
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13 75 wide agreement that informed consent (including parental permission) requires more than a
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16 76 signature on a form: efforts should be put to promote understanding of consent information.¹⁵
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19 77 The Strategic Initiative for Developing Capacity in Ethical Review (SIDCER) has
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22 78 recently proposed the 'enhanced ICF development' methodology, named 'SIDCER ICF', in
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25 79 response to the need for making an ICF complete, concise and understandable.¹⁶ The SIDCER
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28 80 ICF methodology has been tested in real informed consent settings involving several clinical
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31 81 trials and it has been shown to be effective in improving participants' understanding.¹⁷ As such,
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34 82 it is compelling to extend the application of the SIDCER ICF methodology to clinical research
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37 83 requiring proxy consent. Therefore, the present study was designed to test the applicability and
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40 84 effectiveness of the SIDCER ICF in pediatric research requiring parental consent. The
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43 85 objective of this study was to compare the parental understanding of information between the
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46 86 parents who read the SIDCER ICF and those who read the conventional ICF.
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87 **Materials and Methods**

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

93 *Study participants*

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

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

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4 106 This hypothesized effect size was based on the findings in our previous study.¹⁹
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7 107 *Study interventions*
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10 108 The effectiveness of two different ICF interventions on parental understanding were
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13 109 compared: one was the original, standard ICF of the pediatric drug trial (in Thai) and another
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16 110 was the enhanced (SIDCER) ICF of the trial (in Thai). The former comprising six pages with
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19 111 2,065 words was considered as the conventional ICF; trial-related information was described
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22 112 using text in standard sequences. The latter comprising four pages with 1,644 words was
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25 113 developed according to the SIDCER ICF methodology, comprehensively described
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28 114 elsewhere.¹⁶ In brief, essential information as is relevant to the parents' decision making was
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31 115 summarized in the SIDCER ICF template (available from [http://ijme.in/pdf/appendix-](http://ijme.in/pdf/appendix-1.pdf?v=1)
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34 116 [1.pdf?v=1](http://ijme.in/pdf/appendix-1.pdf?v=1)) in a narrative and illustrative manner, according to the SIDCER ICF principles. The
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37 117 drafted SIDCER ICF was, then, reviewed by laypersons to enhance the readability and
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40 118 understandability of written information. Both conventional and SIDCER ICFs contained the
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43 119 same content.
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46 120 *Study outcomes*
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49 121 Parental understanding of essential research-related information was measured using
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52 122 the questionnaire (in Thai), which was modified from our previous studies.^{17,19,20} It consisted
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55 123 of 24 scenario-based questions which assessed parental understanding of relevant ICF content
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58 124 in the following categories: general items (five questions), patient's rights (four questions),
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4 125 scientific aspects (eight questions), and ethics aspects (seven questions). Each question with
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7 126 three possible answers was structured in a way that the parents would have had to apply their
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10 127 understanding of information given in an ICF to the scenario.²¹ In each question, there was
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13 128 only one correct answer, counting as a score of 1, making the highest possible score 24. The
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16 129 primary endpoint was the proportion of parents obtaining the total score of more than 80%
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19 130 ($\geq 20/24$). The secondary endpoints were the total score, the score of each category, and time
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22 131 spent reading a given ICF and completing the questionnaire.

23 24 25 132 *Study procedure*

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28 133 For allocation of the parents, a computer-generated list of random numbers was
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31 134 applied, and a randomization code was packed in an opaque sealed envelope before subject
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34 135 enrollment to this ICF study. Eligible parents were randomly assigned to read either the
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37 136 SIDCER ICF or the conventional ICF. After that, the questionnaire was distributed. The parents
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40 137 could keep and read the ICF while completing the questionnaire, but they could not ask any
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43 138 questions during this process. Time spent reading the given ICF and completing the
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46 139 questionnaire was recorded and this was the end of the ICF study. The informed consent
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49 140 process continued for the clinical trial for both groups in the same manner, that is, informed
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52 141 consent discussion with the parents was conducted and any inaccurate understanding of trial
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55 142 information was explained prior to the parents' decision whether or not to sign consent for their
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58 143 child's participation in the pediatric drug trial.

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4 144 *Patient and public involvement*
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7 145 The present study did not involve patients or publics during the development of
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10 146 research question and outcome measures as well as in the study design and recruitment plan.
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13 147 Patient burden was not assessed formally, but assumed to be low. Results will be disseminated
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16 148 via this publication, with a lay summary of the results in Thai.

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19 149 *Data analysis*
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22 150 Descriptive statistics were used to describe the basic features of the data in this study.
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25 151 The proportion of the parents in the SIDCER ICF group who achieved the outcome divided by
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28 152 that of the conventional ICF group was presented using the term 'relative risk' (RR).
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31 153 Dichotomous variables were compared using χ^2 test. Continuous variables were presented in
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34 154 mean \pm standard deviation (SD), and the values between the two groups were compared using
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37 155 the Student *t*-test. Cohen's *d* was used to classify the effect size as small ($d = 0.2$), medium (d
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40 156 = 0.5), and large ($d = 0.8$).²² Multivariable linear regression analysis was performed to evaluate
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43 157 the relationship between different ICF interventions and the total score after adjusting for age,
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46 158 gender, and education. All statistical analysis was executed using IBM SPSS Statistics for
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49 159 Windows, Version 22.0, with a *p* value of less than 0.05 considered to indicate statistical
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52 160 significance.
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161 **Results**

162 Two hundred and ten parents of thalassemia children were enrolled between
163 September 2015 and September 2016 and equally assigned to the SIDCER ICF group ($n = 105$)
164 and the conventional ICF group ($n = 105$) (Fig. 1). The mean age of 210 enrolled parents was
165 35.6 ± 3.1 years; 72.9% were female, and 61.0% had education at a bachelor degree or higher
166 (Table 1).

167 The primary endpoint was achieved by 42.9% and 27.6% of the parents in the SIDCER
168 ICF group and the conventional ICF group, respectively (RR = 1.552, 95%CI = 1.061 to 2.270,
169 $p = 0.021$). The parents in the SIDCER ICF group obtained higher total scores when compared
170 to the conventional ICF group (total score: 18.07 ± 3.71 vs. 15.98 ± 4.56 , mean difference =
171 2.09 , 95% CI = 0.96 to 3.22, $p < 0.001$). After adjustment for age, gender, and education, a
172 significant difference in the total score between the two groups was still evident (B = 2.75, SE
173 = 0.54, beta = 0.32, 95% CI = 1.69 to 3.81, $p < 0.001$). The values of other secondary endpoints
174 are presented in Table 2.

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

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4 180 understood by the parents in both groups was trial treatment and random assignment; only 66
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7 181 (out of 210) parents (31.4%) answered this element correctly.
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182 **Discussion**

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

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

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4 201 to support that increased processability of key or complex information in an ICF could
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7 202 contribute to a significant improvement in parental understanding of such information.²³
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10 203 The element that was least understood by the parents in both groups was trial treatment
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13 204 and random assignment. This finding supports lines of the evidence demonstrating that there
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16 205 is the apparent universality of a limited understanding on the aspect of random allocation of
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19 206 the intervention in clinical trials.²⁴⁻²⁵ Despite an attempt with increased processability in the
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22 207 SIDCER ICF to aid in description on the concept of randomization (using illustrations and
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25 208 highlights), a large proportion of the parents (63.8%) still did not understand it accurately. This
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28 209 emphasizes the need of increased attention in particular during informed consent discussion to
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31 210 ensure adequate understanding of this concept among individuals who consent to a trial.²⁶ A
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34 211 combination of the SIDCER ICF methodology with other means (*e.g.*, an integrated cognitive
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37 212 approach) may enhance parental understanding of this information in pediatric research.²⁷
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40 213 Although the overall results suggested that the SIDCER ICF was superior to the
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43 214 conventional ICF in this setting, the degree of parental understanding remained unsatisfactory.
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46 215 Deficiencies in understanding were still prevalent even among those who read the SIDCER
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49 216 ICF. Moreover, we have noticed that the level of parental understanding in this study is
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52 217 apparently lower than our observations in the previous ICF studies involving other groups of
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55 218 populations.^{17,19,20} Continued consideration of the normative and practical aspects of informed
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58 219 consent is needed in an attempt to facilitate understanding among parents who act as proxies
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4 220 for their child's participation in research.^{28,29} It may be worthwhile to consider using more
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7 221 graphics or pictographs to enhance visualization of complex information in the SIDCER ICF,³⁰
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10 222 and further research may be required to determine the effectiveness of such additional means,
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13 223 especially in this group of populations. In addition to the enhanced ICF, a dialogue between
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16 224 the investigator (or a person designated by the investigator) and the parents are still
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19 225 indispensable, while complimentary methods of delivering trial-related information (*e.g.*, a
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22 226 multimedia video and website²⁷) may be warranted in some studies. Furthermore, formal
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25 227 evaluation of parental understanding during the process of informed consent may be necessary,
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28 228 especially in pediatric research that poses relatively high risks, with little or no potential direct
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31 229 benefit, to child subjects.^{31,32} Accordingly, any inaccuracy of parental understanding could be
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34 230 rectified to ascertain the validity of parental consent obtained in such research.

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37 231 Of note, this study was confined to parental understanding of an ICF while the child's
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40 232 understanding of an assent form was not studied. It is also possible that the SIDCER ICF
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43 233 methodology may be modified and used to improve the quality of assent forms for pediatric
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46 234 populations. As such, further ICF studies involving pediatric populations are warranted.

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49 235 In conclusion, the present study demonstrated that the SIDCER ICF methodology was
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52 236 applicable to pediatric research requiring parental consent and effective in improving parental
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55 237 understanding of trial information. However, deficiencies in understanding were still prevalent
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58 238 among the parents of child subjects, at least, in this setting, suggesting that further research is
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239 required to improve parental understanding in pediatric research.

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13 243 from laypersons' perspectives.

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16 244 **Contributor:** The study was designed by Nut Koonrungsesomboon and Juntra Karbwang, and
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19 245 conducted by Chanchai Traivaree and Charnunnut Tiyapsane. Data analysis was done by Nut
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22 246 Koonrungsesomboon. The manuscript was written by Nut Koonrungsesomboon and revised
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25 247 by Juntra Karbwang, with contributions from all authors. All authors approved the final version
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27
28 248 submitted.

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40 252 the World Bank, and WHO through the Forum for Ethical Review Committees in the Asian
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46 254 interpretation of the data; preparation, review or approval of the manuscript; and decision to
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49 255 submit this manuscript for publication.

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52 256 **Competing interests:** We have read and understood BMJ policy on declaration of interests
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55 257 and declare that we have no competing interests.

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58 258 **Ethics approval:** This study was approved by the Institutional Review Board of Royal Thai
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4 259 Army Medical Department (No. IRB/RTA1200/2557). Informed consent was obtained by

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10 261 **Data sharing statement:** Deidentified participant data will be available upon reasonable

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13 262 request by contacting the corresponding author.
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339 **Table 1** Demographic data of the parents (*n* = 210)

	SIDCER ICF (<i>n</i> = 105)	Conventional ICF (<i>n</i> = 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%)

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

341 **Table 2** Comparisons of the total score, the score in each category of the ICF content, and time
 342 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

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

344 **Table 3** Comparisons of the parental understanding of each element of the ICF content between
 345 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

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

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4 347 **Figure legends**

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7 348 **Fig. 1** Flow diagram of this ICF study
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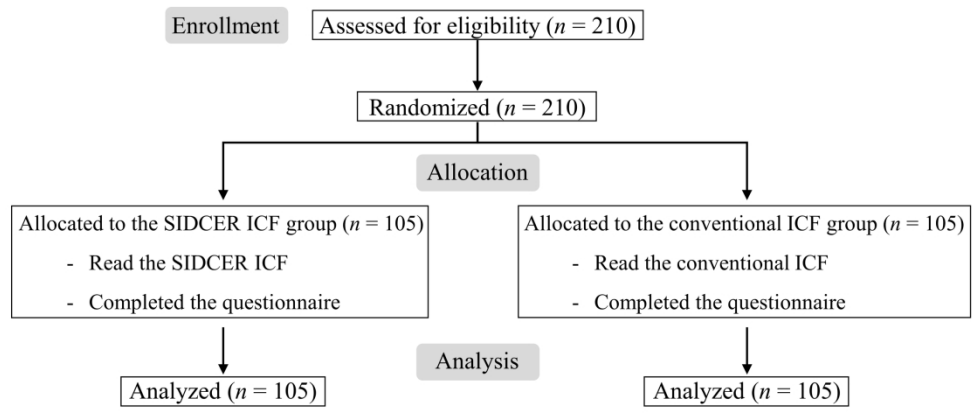


Fig. 1 Flow diagram of this ICF study

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
	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	10

1	Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	n/a
2				
3		11b	If relevant, description of the similarity of interventions	n/a
4	Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	11
5		12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	11
6				
7	Results			
8	Participant flow (a	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and	12
9	diagram is strongly		were analysed for the primary outcome	
10	recommended)	13b	For each group, losses and exclusions after randomisation, together with reasons	n/a
11	Recruitment	14a	Dates defining the periods of recruitment and follow-up	12
12		14b	Why the trial ended or was stopped	n/a
13	Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
14	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
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16	Outcomes and	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its	12-13,
17	estimation		precision (such as 95% confidence interval)	Tables 2
18		17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	12-13
19	Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	12-13,
20				Table 3
21	Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	n/a
22				
23	Discussion			
24	Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	14-16
25	Generalisability	21	Generalisability (external validity, applicability) of the trial findings	14-16
26	Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	14-16
27				
28	Other information			
29	Registration	23	Registration number and name of trial registry	n/a
30	Protocol	24	Where the full trial protocol can be accessed, if available	n/a
31	Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	17

n/a, not applicable