TITLE PAGE

Title:

Improved Participants' Understanding of Research Information in Real Settings Using the SIDCER Informed Consent Form: A Randomized-Controlled Informed Consent Study Nested with Eight Clinical Trials

Concise title:

Improved Participants' Understanding in Eight Clinical Trials

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Abstract

Purpose: This study aimed to test the applicability and effectiveness of the principles and informed consent form (ICF) template proposed by the Strategic Initiative for Developing Capacity in Ethical Review (SIDCER) across multiple clinical trials involving Thai research participants with various conditions.

Methods: A single-center, randomized-controlled study nested with eight clinical trials was conducted at Thammasat University Hospital, Thailand. A total of 258 participants from any of the eight clinical trials were enrolled and randomly assigned to read either the SIDCER ICF (n = 130) or the conventional ICF (n = 128) of the respective trial. Their understanding of necessary information was assessed using the post-test questionnaire; they were allowed to consult a given ICF while completing the questionnaire. The primary endpoint was the proportion of the participants who had the post-test score of ≥80%, and the secondary endpoint was the total score of the post-test.

Results: The proportion of the participants in the SIDCER ICF group who achieved the primary endpoint was significantly higher than that of the conventional ICF group (60.8 vs. 41.4%, $p = 0.002$). The total score of the post-test was also significantly higher among the participants who read the SIDCER ICF than those who read the conventional ICF (83.3 vs. 76.0%, $p < 0.001$).

Conclusions: The present study demonstrated that the SIDCER ICF was applicable and effective to improve Thai research participants' understanding of research information in diverse clinical trials. Using the SIDCER ICF methodology, clinical researchers can improve the quality of ICFs for their trials.

Keywords: Informed consent; Consent forms; Comprehension; Understanding; Clinical trials; Clinical studies.

Introduction

Several clinical trials have faced with the challenge of a limited, suboptimal understanding of necessary trial-related information among research subjects [1-4]. Some subjects may enter a trial unaware of foreseeable risks and of the fact that they are taking part in research [5, 6]. They may unintentionally violate the study protocol due to insufficient understanding, affecting the validity and reliability of results obtained [7].

A written informed consent form (ICF) is mandatory and essential in most clinical studies as it is a primary vehicle for disclosure of research information and documentation of subjects' consent according to international ethical guidelines and regulations [8-10]. Therefore, it should contain adequate and relevant information for the subjects' decision making in a concise and simple language [11]. However, the observation of the current practice shows that the ICFs used in contemporary clinical trials have been lengthened over time [12, 13], and many of them are complicated, poorly organized, incomprehensible, incomplete, or even misinformed [14-17]. A recent systematic review and meta-analysis on informed consent demonstrates no increased proportion of research subjects who have an optimal understanding of trial information over 30 years [18].

In an attempt to address concerns on the quality of ICFs, the Strategic Initiative for Developing Capacity in Ethical Review (SIDCER) – an international network, launched by World Health Organization – has recently proposed principles and a guideline for the development of an enhanced ICF, named "SIDCER ICF" [19]. The first validation was performed in Thai volunteers where the SIDCER ICF methodology was applied to a clinical pharmacokinetics drug-drug interaction study involving healthy subjects [20]. The results

demonstrated that the SIDCER ICF improved the participants' understanding, when compared to the conventional ICF [20]. Further investigations in different types of research studies and settings are required to confirm its applicability and effectiveness.

This study aimed to test the applicability and effectiveness of the SIDCER ICF methodology across multiple clinical trials involving Thai populations with diverse conditions in actual informed consent processes. We hypothesized that the SIDCER ICF would be superior to the conventional ICF in obtaining the participants' optimal understanding of trial information.

Methods

This study (hereafter referred as "ICF study") was a single-center, open-label, randomized-controlled study of the two different ICF interventions (1:1), i.e., the SIDCER ICF and the conventional ICF, using a post-test questionnaire as an assessment tool. The ICF study was conducted at Thammasat University Hospital, Pathum Thani, Thailand. The ICF study protocols and all related documents were approved by the Human Ethics Committee of Thammasat University. The ICF study was registered in the WHO registry network as ChiCTR-TRC-14004817.

Recruitment of collaborating studies

Clinical trials that were planned to be conducted at Thammasat University Hospital during May 2014 to April 2016 were assessed for study eligibility based on predefined criteria: (1) a study with an intervention(s) involving human subjects aged >18 years old that its protocol had been approved by the Human Ethics Committee of Thammasat University; (2) a study with the planned number of subjects involved of at least 10 individuals at Thammasat University Hospital; (3) a study not involving patients with a psychological, neurological or visual disorder; (4) a study having a written ICF approved; and (5) a study that the investigators (hereafter referred as "collaborating investigators") agreed to collaborate and involve in the ICF study. Clinical trials that met all the above criteria were recruited and are hereafter referred as "collaborating studies." The ICF study investigators provided the collaborating investigators with administrative assistance during the process of protocol amendments required to embed the ICF study into a collaborating study (see below). The

collaborating investigators could initiate patient enrollment for their trial using the approved conventional ICF without the delay as a result of protocol modification and resubmission of the amendments to the research ethics committee for approval (Fig. 1).

Protocol amendments of collaborating studies

The protocols of collaborating studies were undergone an amendment for the informed consent process: (1) the use of any of the two ICF interventions (see below) by random assignment and (2) the process of the subjects' understanding assessment using the post-test questionnaire (see below). The amended informed consent process provided an option for all prospective subjects of collaborating studies to make a voluntary decision whether to participate in the ICF study. Eligible subjects of collaborating studies who chose not to participate in the ICF study would undergo the conventional process of informed consent using the conventional ICF and needed not to perform the post-test questionnaire. The amended protocols were then submitted to the Human Ethics Committee of Thammasat University for review and approval.

ICF interventions: the SIDCER ICF and the conventional ICF

An original ICF (in Thai) of each collaborating study which had been approved by the Human Ethics Committee of Thammasat University prior to the ICF study recruitment was considered as a conventional ICF and used as a control in this ICF study.

A SIDCER ICF (in Thai) of each collaborating study was developed following the SIDCER ICF methodology extensively described elsewhere [19]. In brief, the protocol of each collaborating study was reviewed and the essential information was selected and synthesized; then, information as is relevant to the study participants' decision making on whether to participate in the collaborating study was included in the SIDCER ICF template (available from: http://ijme.in/pdf/appendix-1.pdf?v=1) in a narrative and illustrative manner, where appropriate. The SIDCER ICF of each collaborating study was reviewed by the respective collaborating investigator(s) to ensure the accuracy of the information presented and by independent laypersons to improve the readability and understandability of the SIDCER ICF. It was submitted together with the respective amended protocol to the Human Ethics Committee of Thammasat University for review and approval.

Assessment tool: the post-test questionnaire

The post-test questionnaire (in Thai) used in previous studies [20, 21] was modified to include study specific information of each collaborating study. The questionnaire consisted of 25 short case scenarios or less, based on the nature of each collaborating study. One scenario addressed one required element of the ICF content using a common practical situation relevant to the study, and a question with three possible answers was structured in a way that the participants would have had to apply their understanding of the information given to the scenario. Each of these ICF mandatory elements per regulatory was necessary for the individuals' rational decision of whether participation in the trial was consistent with their interests and preferences. The

questionnaire of each collaborating study was reviewed and corrected by the respective collaborating investigator(s) and independent laypersons. It was then submitted to the Human Ethics Committee of Thammasat University for review and approval.

Study endpoints

The primary endpoint was the proportion of the participants who had the post-test score of ≥80%. The secondary endpoints were the total score of the post-test, the score of each category of the elements required, and the time spent for reading a given ICF and completing the post-test questionnaire.

Sample size determination

The number of 250 subjects was required to detect the 20% difference between two independent proportions of the primary endpoint ($p_1 = 0.8$ and $p_2 = 0.6$) with the precision and confidence level of 95% ($\alpha = 0.05$), 80% power ($1 - \beta = 0.8$), and the allocation ratio of 1, using a continuity correction with an estimate of 20% for missing data. The estimated sample size was calculated using G*power 3.1.9.2 for Windows.

Study procedure

Prospective patients who were invited to take part in each collaborating study or their representatives, when necessary, were invited to participate in the ICF study. Individuals who declined to participate in the ICF study or cannot read and write Thai were excluded. The ICF study was carried out in an anonymous manner

using a subject number given, and none of identifiable or health-related information was collected. Informed consent was obtained verbally from all individual participants prior to their participation in the ICF study.

The two main processes of this ICF study included (1) the process of reading a given ICF and (2) the process of doing the post-test questionnaire. In each collaborating study, the prospective subjects or their representatives, when necessary, were enrolled sequentially and randomly assigned to read either the SIDCER ICF or the conventional ICF, using a predetermined computer-generated randomization list. Eligible individuals could read a given ICF and ask any inquiry until their satisfaction; then, the post-test questionnaire was distributed. They were allowed to keep and read the ICF while completing the questionnaire. The time spent on the two processes was recorded. After the post-test, the participants were corrected any inaccurate understanding of the trial information prior to their decision to participate in a respective parent clinical study.

Data analysis

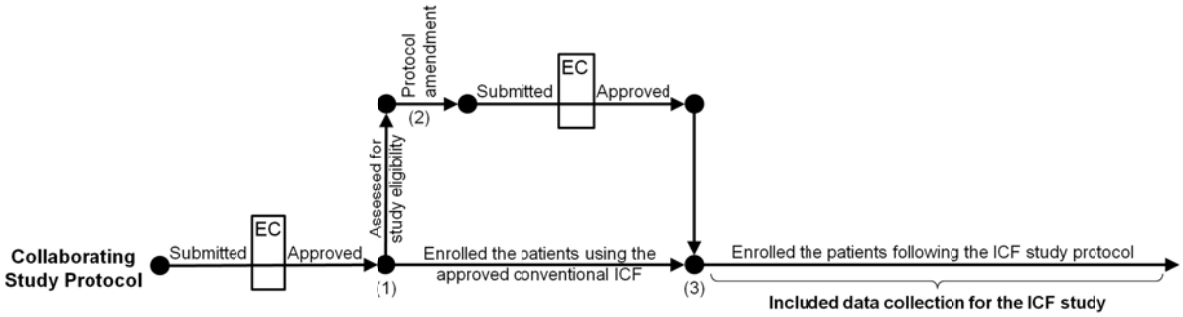
A correct or incorrect answer of each question in the post-test questionnaire was counted as a score of 1 or 0, respectively. For each collaborating study, the total score of the post-test and the score of each category of the ICF elements required were calculated and converted into a percentage. Data from all collaborating studies were assembled, and the predefined endpoints of this ICF study were then analyzed.

The chi-squared test or the Fisher exact test, where appropriate, was applied for the comparison of nominal data between the two groups. The Wilcoxon rank sum test was used for the comparison of interval data between the two groups as none of the data was normally distributed. The endpoints were adjusted by

calculating a percentage of the score from only the questions of which description of the corresponding elements were available in both ICF interventions of a collaborating study. This "adjusted endpoints" aimed to determine the effectiveness of the linguistics and presentational means used in the two different ICFs, exclusive of the lack of certain information in the conventional ICF. The chi-squared test and the Kruskal-Wallis test were applied to check for differences of nominal data and interval data, respectively, among collaborating studies. Subgroup analyses were performed by applying the chi-squared test or the Fisher exact test, where appropriate, to determine the impact of gender (male and female) generation (generation Y, individuals whose age was up to 34 years at an enrollment date; generation X, individuals whose age was between 35 and 51 years; and baby boomers, individuals whose age was over 52 years) and educational level (level 1, high school or lower; level 2, bachelor degree or equivalent; and level 3, master/doctoral degree or equivalent) on the primary endpoint. The multivariate analysis was performed to identify any associations between demographic variables and the primary outcome.

A statistical significance was set at $\alpha = 0.05$ for all tests. Statistical analysis was performed using standard statistical software (SPSS version 22.0). Figures were generated using GraphPad Prism version 5.0 or Microsoft PowerPoint 2007.

Fig. 1 Approach for study recruitment



(1) The ICF study investigators approached an approved clinical study protocol and assessed for study eligibility. (2) If eligible, the ICF study investigators prepared a protocol amendment and related materials (i.e., the SIDCER ICF and the post-test questionnaire) for the recruited study. After reviewed and corrected by the collaborating investigator(s), the amended protocol and materials were submitted to the research ethics committee (EC) for approval. (3) The collaborating investigators enrolled prospective patients using any of the two ICF interventions (the SIDCER ICF or the conventional ICF) by random assignment, followed by the understanding assessment using the post-test questionnaire. During the period of protocol modification and resubmission for ethical approval, the collaborating investigators could enroll prospective patients using the approved conventional ICF.

Results

Eight clinical trials met the ICF study recruitment criteria and were coded as study 1 to study 8. The features of eight collaborating studies are given in Table 1: All were investigator-initiated, randomized-controlled trials. The median page length of the SIDCER ICFs was significantly shorter than that of the conventional ICFs (4 pages vs. 7.5 pages, $p = 0.001$; 1,502 words vs. 2,542 words, $p = 0.012$).

Of 286 individuals who were invited to participate in any of the eight collaborating studies during the ICF study period, a total of 258 participants (aged 50.5 ± 15.2 years) were enrolled into this ICF study. One hundred and thirty participants were randomly assigned to the SIDCER ICF group, while the others to the conventional ICF group (Fig. 2). Their demographic data are shown in Table 2: 61.2% were female, 53.9% were under the baby boomers generation, and 52.7% had educational level 1.

In the SIDCER ICF group, 60.8% of the participants (79/130) achieved the primary endpoint, compared to 41.4% (53/128) in the conventional ICF group (RR = 1.468, 95% CI = 1.145-1.881, $p = 0.002$) (Fig. 3). There was also a significantly higher proportion of the participants in the SIDCER ICF group who achieved the adjusted primary endpoint, when compared to that of the conventional ICF group (64.6 vs. 50.8%, RR = 1.272, 95% CI = 1.029-1.574, $p = 0.024$). In the SIDCER ICF group, there was no statistically significant difference among eight collaborating studies for the proportions of the participants who achieved the primary endpoint ($\chi^2(7) = 6.672$, $p = 0.464$), while a significant difference was seen in the conventional ICF group ($\chi^2(7) = 35.311$, $p < 0.001$).

Subgroup analyses on the primary endpoint demonstrated that male participants, the participants

under the baby boomers generation, and the participants who had educational level 1 statistically significantly favored the SIDCER ICF (Fig. 3). The post hoc analyses demonstrated a power of test (1-β) of 23.9, 5.2, 9.5, 12.5, and 4.1% in female participants, the participants under the generation Y and the generation X, and the participants who had educational level 2 and level 3, respectively. The multivariate analysis demonstrated that education and age were significantly associated with the primary endpoint (OR = 4.42, 95%CI = 2.62-7.47, $p <$ 0.001; OR = 0.97, 95%CI = 0.95-0.99, $p = 0.001$, respectively).

The assessment of the secondary endpoints showed that the total score of the post-test and the score of scientific aspects in the SIDCER ICF group were significantly higher than those of the conventional ICF group (83.3 vs. 76.0%, $p < 0.001$; and 87.5 vs. 75.0%, $p < 0.001$, respectively), whereas there was no statistical difference between the two groups for the scores of the other aspects and the time spent (Table 3). The adjusted total score of the post-test in the SIDCER ICF group was also significantly higher than that of the conventional ICF group (86.0 vs. 80.5%, $p = 0.002$). The SIDCER ICF group had no statistically significant difference among eight collaborating studies for the total score ($\chi^2(7) = 6.766$, $p = 0.454$), whereas a significant difference was noted in the conventional ICF group ($\chi^2(7) = 41.643$, $p < 0.001$).

Comparative proportions of the participants who correctly answered each item in the post-test questionnaire between the two groups showed significant differences in seven (out of 25) items (Fig. 4). The SIDCER ICF was superior to the conventional ICF in improving the participants' understanding on the following elements: the foreseeable risks ($p = 0.046$), the purpose of the study ($p = 0.029$), trial treatment (i.e., randomization and the use of placebo, if applicable) ($p = 0.012$), identification of any experimental procedures

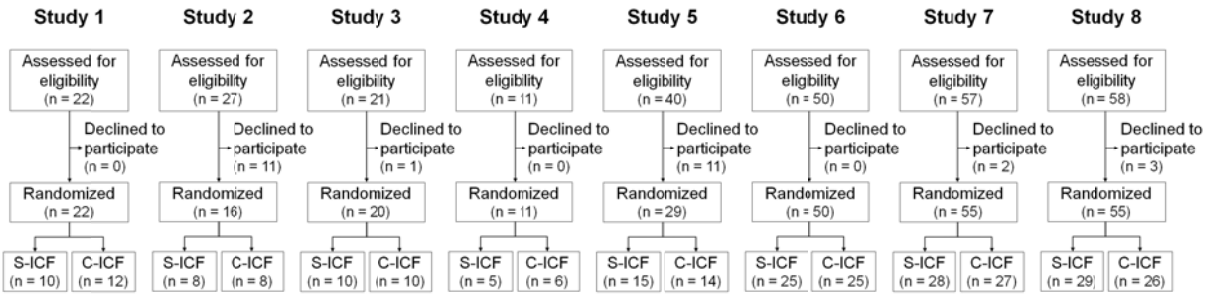
($p = 0.047$), who can access the data ($p = 0.025$), the duration of the subject's participation ($p = 0.006$), and the number of subjects required ($p < 0.001$).

Table 1 Characteristics of the collaborating studies

Study	Condition of the patients	Age (years)	Study design	Intervention under investigation	Clinical phase	SIDCER ICF		Conventional ICF	
						Pages	Words	Pages	Words
1	Dyslipidemia	35-65	Double-blind, randomized, controlled	Herbal drug vs. Simvastatin	II	4	1657	8	2940
2	Dyslipidemia	18-70	Double-blind, randomized, controlled	Herbal drug vs. Simvastatin	II	4	1654	8	2353
3	Osteoarthritis of the knee	50-85	Double-blind, randomized, controlled	Anti-inflammatory agent vs. Placebo	IV	5	1442	5	1554
4	Osteoarthritis of the knee	50-85	Double-blind, randomized, controlled	One surgical intervention vs. another surgical intervention	n/a	5	1436	5	1500
5	Allergic rhinitis	20-60	Double-blind, randomized, controlled	Herbal drug vs. Loratadine	II	4	1558	8	2731
6	Hepatocellular carcinoma	18-65	Double-blind, randomized, controlled	Hepatoprotective agent vs. Placebo	III	4	1434	5	2273
7	Dyspepsia	18-70	Open-label, randomized, controlled	Modified standard triple therapy regimen vs. sequential therapy regimen	IV	4	1589	9	3477
8	Elective surgery	18-80	Double-blind, randomized, controlled	Herbal drug vs. Placebo	II	4	1446	7	2930

n/a, not applicable

Fig. 2 Flow diagram of the collaborating studies



Two hundred and fifty-eight participants from eight collaborating studies were enrolled: 130 were assigned to the SIDCER ICF (S-ICF) group, while 128 to the conventional ICF (C-ICF) group.

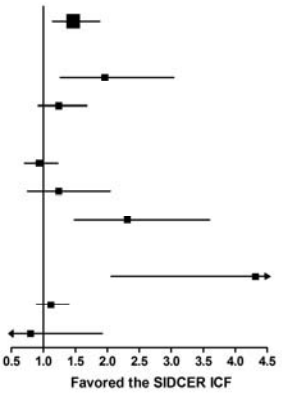
Table 2 Demographic data of the participants (n = 258)

	SIDCER ICF (n = 130)		Conventional ICF (n = 128)	
Sex				
Male	49	(37.7%)	51	(39.8%)
Female	81	(62.3%)	77	(60.2%)
Generation				
Generation Y	23	(17.7%)	25	(19.5%)
Generation X	38	(29.2%)	33	(25.8%)
Baby Boomers	69	(53.1%)	70	(54.7%)
Education				
Level 1	73	(56.2%)	63	(49.2%)
Level 2	54	(41.5%)	59	(46.1%)
Level 3	3	(2.3%)	6	(4.7%)

Data represent the number of participants. Generation was divided into three subgroups: (1) Generation Y includes participants whose age was up to 34 years at an enrollment date, (2) generation X includes participants whose age was between 35 and 51 years, and (3) baby boomers includes participants whose age was over 52 years. Education was divided into three levels: Level 1 represents high school level or lower, level 2 represents bachelor degree or equivalent, and level 3 represents master/doctoral degree or equivalent.

Fig. 3 Comparisons of the primary endpoint between the two groups

	SIDCER ICF		Conventional ICF		Relative Risk* (95%CI)		*P* value
All	79/130	(60.8%)	53/128	(41.4%)	1.468	(1.145-1.881)	**0.002**
Sex							
Male	32/49	(65.3%)	17/51	(33.3%)	1.959	(1.264-3.038)	**0.001**
Female	47/81	(58.0%)	36/77	(46.8%)	1.241	(0.918-1.678)	0.156
Generation							
Generation Y	18/23	(78.3%)	21/25	(84.0%)	0.932	(0.708-1.227)	0.719
Generation X	20/38	(52.6%)	14/33	(42.4%)	1.241	(0.753-2.043)	0.390
Baby Boomers	41/69	(59.4%)	18/70	(25.7%)	2.311	(1.483-3.600)	**<0.001**
Education							
Level 1	35/73	(47.9%)	7/63	(11.1%)	4.315	(2.062-9.028)	**<0.001**
Level 2	42/54	(77.8%)	41/59	(69.5%)	1.119	(0.897-1.396)	0.319
Level 3	2/3	(66.7%)	5/6	(83.3%)	0.800	(0.333-1.922)	1.000



Data represent the proportion of the participants whose post-test score was satisfied according to the 80% passing level. Relative risk is the ratio derived from the proportion of the SIDCER ICF group divided by that of the conventional ICF group (*asterisk*).

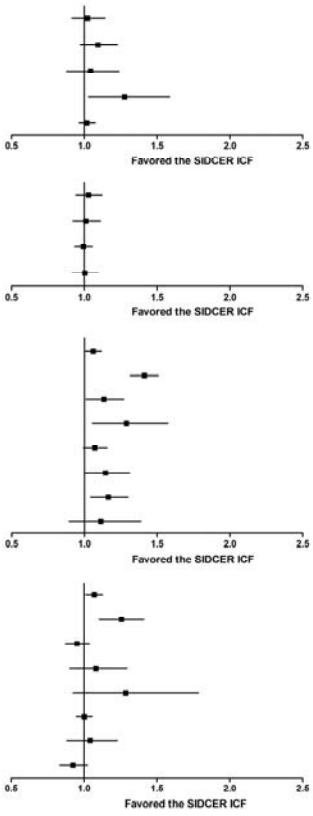
Table 3 Comparisons of the secondary endpoints between the two groups

	SIDCER ICF (n = 130)		Conventional ICF (n = 128)		*P* value
Total score (%)	83.3	(75.0-91.7)	76.0	(66.7-87.5)	**<0.001**
General aspects (%)	60.0	(60.0-80.0)	60.0	(60.0-80.0)	0.380
Rights aspects (%)	100.0	(100.0-100.0)	100.0	(75.0-100.0)	0.481
Scientific aspects (%)	87.5	(75.0-100.0)	75.0	(62.5-87.5)	**<0.001**
Ethical aspects (%)	75.0	(62.5-87.5)	75.0	(62.5-87.5)	0.410
Time (min)	30.0	(20.0-50.0)	30.0	(20.0-40.0)	0.959

Data represent the median (interquartile, Q_1-Q_3) of the total score of the post-test, the score in each category of the ICF elements, and the time spent for reading a given ICF and completing the post-test questionnaire. Bold entries indicate statistical significance (p value < 0.05).

Fig. 4 Comparisons of the participants' understanding of each ICF element between the two groups

	SIDCER ICF		Conventional ICF		Relative Risk* (95%CI)		*P* value
General items							
Recognition that this is research	109/130	(83.8%)	105/128	(82.0%)	1.022	(0.915-1.142)	0.698
Subjects' responsibility	111/130	(85.4%)	100/128	(78.1%)	1.093	(0.973-1.227)	0.131
Confidentiality of records	89/130	(68.5%)	84/128	(65.6%)	1.043	(0.879-1.238)	0.628
Who can access the data	83/130	(63.8%)	64/128	(50.0%)	1.277	(1.029-1.585)	**0.025**
Research contact persons	125/130	(96.2%)	121/128	(94.5%)	1.017	(0.964-1.074)	0.536
Rights of the subject							
Right to refuse	117/130	(90.0%)	112/128	(87.5%)	1.029	(0.943-1.122)	0.525
Right to withdraw	114/130	(87.7%)	111/128	(86.7%)	1.011	(0.921-1.110)	0.815
Consequences of withdrawal	122/130	(93.8%)	121/128	(94.5%)	0.993	(0.934-1.055)	0.814
Right to receive new information	91/100	(91.0%)	88/97	(90.7%)	1.003	(0.918-1.096)	0.946
Scientific aspects							
Eligibility of the subject	117/130	(90.0%)	109/128	(85.2%)	1.057	(0.964-1.159)	0.238
Number of subjects required	127/130	(97.7%)	89/128	(69.5%)	1.405	(1.249-1.580)	**<0.001**
Purpose of the study	114/130	(87.7%)	99/128	(77.3%)	1.134	(1.012-1.270)	**0.029**
Trial treatment	89/130	(68.5%)	68/128	(53.1%)	1.289	(1.055-1.574)	**0.012**
Trial procedures	123/130	(94.6%)	113/128	(88.3%)	1.072	(0.994-1.156)	0.069
Identification of any experimental procedures	97/115	(84.3%)	84/114	(73.7%)	1.145	(1.000-1.310)	**0.047**
Duration of the subject's participation	117/130	(90.0%)	99/128	(77.3%)	1.164	(1.043-1.299)	**0.006**
Storage and/or reuse of human materials	59/86	(68.6%)	53/86	(61.6%)	1.113	(0.894-1.387)	0.337
Ethical aspects							
Alternative procedure or course of treatment	117/130	(90.0%)	108/128	(84.4%)	1.067	(0.971-1.172)	0.176
Foreseeable risks	83/130	(63.8%)	66/128	(51.6%)	1.238	(1.002-1.531)	**0.046**
Expected direct and/or indirect benefits	113/130	(86.9%)	117/128	(91.4%)	0.951	(0.873-1.036)	0.247
Post-trial benefits	81/115	(70.4%)	73/112	(65.2%)	1.081	(0.903-1.294)	0.397
Criteria for the termination of participation	48/102	(47.1%)	37/101	(36.6%)	1.285	(0.925-1.785)	0.132
Prorated payment for participation	124/130	(95.4%)	122/128	(95.3%)	1.001	(0.948-1.056)	0.978
Anticipated expenses	91/130	(70.0%)	86/128	(67.2%)	1.042	(0.883-1.229)	0.626
Compensation for injury	106/130	(81.5%)	113/128	(88.3%)	0.924	(0.833-1.024)	0.131



Data represent the proportion of the participants who correctly answered each item in the post-test questionnaire.

Relative risk is the ratio derived from the proportion of the SIDCER ICF group divided by that of the conventional ICF group (*asterisk*).

Discussion

The present ICF study nested with eight clinical trials validated the applicability of the SIDCER ICF methodology in the development of enhanced ICFs for various clinical trials. Significant improvement of the participants' understanding indicates the effectiveness of the SIDCER ICF in the real informed consent process among Thai populations with diverse conditions. This is supported by (1) a significantly higher proportion of the participants who achieved the satisfactory level of understanding at 80% and a higher median score of the post-test in the SIDCER ICF group, when compared to the conventional ICF group, and (2) no statistically significant difference of these two main values in the SIDCER ICF group among eight collaborating studies. Not only was the necessary information provided complete, the linguistics and presentational means used in the SIDCER ICF also contributed to the superiority of the SIDCER ICF over the conventional ICF regarding the participants' understanding, as demonstrated by the adjusted endpoints.

Given that the present study was designed to test the applicability and effectiveness of the SIDCER ICF methodology in actual clinical trials, it rises above the limitation of the previous simulation study in a mock population [20] and provides stronger evidence to support the value of the SIDCER ICF methodology in enhancing subjects' understanding of trial-related information in various clinical research. This study addresses a common pitfall consistently raised by two systematic reviews on informed consent interventions that enhanced ICFs are commonly effective in a fictitious situation, while a few studies demonstrate the superiority of enhanced ICFs in a realistic setting [22, 23].

The success of collaboration with eight clinical trials at Thammasat University Hospital made the

validation of the SIDCER ICF methodology in real settings possible. This was partly attributable to an innovative approach of the present study proposal for study recruitment. Literature notes that trial investigators may be reluctant to team up with the ICF study investigators if collaborations are too burdensome or defer their trial initiation [24, 25]. Our approach reduced administrative burden of collaborating investigators and did not delay their trial enrollment (Fig. 1). We demonstrated that embedding an informed consent study into many clinical trials is feasible.

The present study demonstrated that the SIDCER ICF could do better particularly in scientific aspects of the clinical studies. Five out of seven items in which the results significantly favored the SIDCER ICF belonged to scientific aspects (Fig. 4), including randomization and the use of placebo which is a difficult concept for laypersons to understand [18, 26]. This indicates that the SIDCER ICF provided clearer information that helped the participants understand and interpret scientific matters of the collaborating studies more accurately, when compared to the conventional ICF.

The SIDCER ICF methodology was proven suitable and effective to research participants with advanced age or low educational level. This is supported by the significantly improved understanding of the participants under the baby boomers generation and those with educational level 1 using the SIDCER ICF. In clinical research, investigators and research ethics committees may take note of or be aware of a limited understanding of research subjects with advanced age or low educational level as the evidence suggests [18, 22, 27]. Therefore, the application of the SIDCER ICF methodology could be helpful to address this concern and could ensure or increase the validity of consent obtained from those groups of populations. However, the

superiority of the SIDCER ICF over the conventional ICF in other subgroups requires further investigations because the results of the present study remained inconclusive, as demonstrated by the post hoc analysis for a power of test.

Although the SIDCER ICF was proven superior to the conventional ICF, there is still room for improvement of the SIDCER ICF development. It may be worthwhile to consider using more graphic displays to increase visualization or simplification of some difficult aspects of the study (e.g., a pictograph format for depicting foreseeable risks) [28] or utilizing techniques for improving processability (e.g., larger font for a study involving a geriatric population) [29]. A dialog and discussion between investigators, or qualified persons designated by the investigators, and prospective subjects are still indispensible, while consideration of other modes of information delivery (e.g., multimedia) during an informed consent process may be warranted in some cases [30, 31].

It should be noted that the inherent weakness of an ICF study nested with several clinical trials is the variation of the conventional ICFs' quality used as a control in different collaborating studies. This could result in diverse effectiveness values in a comparative group, as demonstrated by multiple comparisons of the endpoints in the conventional ICF group of this study. Reducing or limiting a number of clinical trials involved may decrease the heterogeneity of the effectiveness values in a control group among collaborating studies. However, study recruitment strategies may require modifications and target only large clinical trials in order to achieve the adequate number of subjects required for testing hypotheses of an informed consent study in a real setting. Future studies on comparative informed consent interventions should take into account the study

recruitment strategies and an appropriate number of collaborating studies involved.

Conclusions

The SIDCER ICF improved the understanding of the participants in this study nested in the actual informed consent processes of eight clinical trials conducted at Thammasat University Hospital. This demonstrates the applicability and effectiveness of the SIDCER ICF principles and template for enhancing the quality of ICFs and improving the subjects' understanding in real research settings. Further studies to assess its applicability and effectiveness in different languages and settings and in other groups of populations (e.g., vulnerable populations) are warranted.

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Authors' contributions

NK designed the study, developed the ICF study protocol and related materials, analyzed the data, interpreted the results, and prepared a drafted manuscript. TT designed the study, developed the ICF study protocol and related materials, conducted and collaborated the study, collected the data, and provided comments for manuscript improvement. KP, RV, SM, PC, SS, TP, SK, NT, RY, WC, RK, SN, and PK provided the collaborating study protocols and the conventional ICFs, reviewed the materials, conducted the study, and collected the data. PS reviewed the ICF study protocol and related materials, and collaborated the study. JK

designed the study, developed the ICF study protocol and related materials, analyzed the data, interpreted the results, and finalized the manuscript.

Compliance with ethical standards

All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Conflict of interest

The authors declare that they have no conflict of interest.

References

1 Molyneux CS, Peshu N, Marsh K (2004) Understanding of informed consent in a low-income setting: three case studies from the Kenyan Coast. Soc Sci Med 59 (12): 2547-2559. doi: 10.1016/j.socscimed.2004.03.037

2 Manafa O, Lindegger G, Ijsselmuiden C (2007) Informed consent in an antiretroviral trial in Nigeria. Indian J Med Ethics 4 (1): 26-30

3 Mandava A, Pace C, Campbell B, Emanuel E, Grady C (2012) The quality of informed consent: mapping the landscape. A review of empirical data from developing and developed countries. J Med Ethics 38 (6): 356-365. doi: 10.1136/medethics-2011-100178

4 Hill Z, Tawiah-Agyemang C, Odei-Danso S, Kirkwood B (2008) Informed consent in Ghana: what do participants really understand? J Med Ethics 34 (1): 48-53. doi: 10.1136/jme.2006.019059

5 Bergenmar M, Molin C, Wilking N, Brandberg Y (2008) Knowledge and understanding among cancer patients consenting to participate in clinical trials. Eur J Cancer 44 (17): 2627-2633. doi: 10.1016/j.ejca.2008.08.013

6 Pentz RD, White M, Harvey RD, Farmer ZL, Liu Y, Lewis C, Dashevskaya O, Owonikoko T, Khuri FR (2012) Therapeutic misconception, misestimation, and optimism in participants enrolled in phase 1 trials. Cancer 118 (18): 4571-4578. doi: 10.1002/cncr.27397

7 Lansimies-Antikainen H, Pietila AM, Laitinen T, Kiviniemi V, Rauramaa R (2010) Is informed consent related to success in exercise and diet intervention as evaluated at 12 months? DR's EXTRA study.

BMC Med Ethics 11: 9. doi: 10.1186/1472-6939-11-9

8 World Medical Association (2013) World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 310 (20): 2191-2194. doi: 10.1001/jama.2013.281053

9 European Medicines Agency. ICH Topic E6 (1996) Guideline for Good Clinical Practice. http://www.edctp.org/fileadmin/documents/EMEA_ICH-GCP_Guidelines_July_2002.pdf. Accessed 20 June 2016

10 Code of Federal Regulations. Title 45 Public Welfare, Part 46 Protection of Human Subjects. https://www.hhs.gov/ohrp/sites/default/files/ohrp/policy/ohrpregulations.pdf. Accessed 20 June 2016

11 Wilkinson S (2010) Consent. In: European Textbook on Ethics in Research. Publications Office of the European Union, Luxembourg, pp 33-48

12 Berger O, Grønberg BH, Sand K, Kaasa S, Loge JH (2009) The length of consent documents in oncological trials is doubled in twenty years. Ann Oncol 20 (2): 379-385. doi: 10.1093/annonc/mdn623

13 Beardsley E, Jefford M, Mileshkin L (2007) Longer consent forms for clinical trials compromise patient understanding: so why are they lengthening? J Clin Oncol 25 (9): e13-14. doi: 10.1200/JCO.2006.10.3341

14 Paasche-Orlow MK, Taylor HA, Brancati FL (2003) Readability standards for informed-consent forms as compared with actual readability. N Engl J Med 348 (8): 721-726. doi: 10.1056/NEJMsa021212

15 Terranova G, Ferro M, Carpeggiani C, Recchia V, Braga L, Semelka RC, Picano E (2012) Low quality

and lack of clarity of current informed consent forms in cardiology: how to improve them. JACC Cardiovasc Imaging 5 (6): 649-655. doi: 10.1016/j.jcmg.2012.03.007

16 Kundapura SV, Poovaiah T, Ghooi RB (2013) The big Cs of the informed consent form: compliance and comprehension. Indian J Med Ethics 10 (4): 232-237

17 Nair SC, Ibrahim H (2015) GCP compliance and readability of informed consent forms from an emerging hub for clinical trials. Perspect Clin Res 6 (2): 104-108. doi: 10.4103/2229-3485.154012

18 Tam NT, Huy NT, Thoa lT, Long NP, Trang NT, Hirayama K, Karbwang J (2015) Participants' understanding of informed consent in clinical trials over three decades: systematic review and meta-analysis. Bull World Health Organ 93 (3): 186-198H. doi: 10.2471/BLT.14.141390

19 Koonrungsesomboon N, Laothavorn J, Chokevivat V, Hirayama K, Karbwang J (2016) SIDCER informed consent form: principles and a developmental guideline. Indian J Med Ethics 1 (2): 83-6

20 Koonrungsesomboon N, Teekachunhatean S, Hanprasertpong N, Laothavorn J, Na-Bangchang K, Karbwang J (2016) Improved participants' understanding in a healthy volunteer study using the SIDCER informed consent form: a randomized-controlled study. Eur J Clin Pharmacol 72 (4): 413-421. doi: 10.1007/s00228-015-2000-2

21 Koonrungsesomboon N, Laothavorn J, Karbwang J (2015) Understanding of Essential Elements Required in Informed Consent Form among Researchers and Institutional Review Board Members. Trop Med Health 43 (2): 117-122. doi: 10.2149/tmh.2014-36

22 Flory J, Emanuel E (2004) Interventions to improve research participants' understanding in informed

consent for research: a systematic review. JAMA 292 (13): 1593-1601. doi: 10.1001/jama.292.13.1593

23 Nishimura A, Carey J, Erwin PJ, Tilburt JC, Murad MH, McCormick JB (2013) Improving understanding in the research informed consent process: a systematic review of 54 interventions tested in randomized control trials. BMC Med Ethics 14: 28. doi: 10.1186/1472-6939-14-28

24 Sachs GA, Hougham GW, Sugarman J, Agre P, Broome ME, Geller G, Kass N, Kodish E, Mintz J, Roberts LW, Sankar P, Siminoff LA, Sorenson J, Weiss A (2003) Conducting empirical research on informed consent: challenges and questions. IRB Suppl 25 (5): S4-S10

25 Kass NE, Taylor HA, Ali J, Hallez K, Chaisson L (2015) A pilot study of simple interventions to improve informed consent in clinical research: feasibility, approach, and results. Clin Trials 12 (1): 54-66. doi: 10.1177/1740774514560831

26 Featherstone K, Donovan JL (1998) Random allocation or allocation at random? Patients' perspectives of participation in a randomised controlled trial. BMJ 317 (7167): 1177-1180

27 Sanchini V, Reni M, Calori G, Riva E, Reichlin M (2014) Informed consent as an ethical requirement in clinical trials: an old, but still unresolved issue. An observational study to evaluate patient's informed consent comprehension. J Med Ethics 40 (4): 269-275. doi: 10.1136/medethics-2012-101115

28 Tait AR, Voepel-Lewis T, Zikmund-Fisher BJ, Fagerlin A (2010) Presenting research risks and benefits to parents: does format matter? Anesth Analg 111 (3): 718-723. doi: 10.1213/ANE.0b013e3181e8570a

29 Tait AR, Voepel-Lewis T, Nair VN, Narisetty NN, Fagerlin A (2013) Informing the uninformed: optimizing the consent message using a fractional factorial design. JAMA Pediatr 167 (7): 640-646.

doi: 10.1001/jamapediatrics.2013.1385

30 Tait AR, Voepel-Lewis T (2015) Digital multimedia: a new approach for informed consent? JAMA 313 (5): 463-464. doi: 10.1001/jama.2014.17122

31 Cohn E, Larson E (2007) Improving participant comprehension in the informed consent process. J Nurs Scholarsh 39 (3): 273-280. doi: 10.1111/j.1547-5069.2007.00180.x