Establishing Best Practices for Translating Informed Consent Forms

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OBJECTIVE

The objective of this poster presentation is to establish best practices for both sponsors and language service providers in the creation and translation of informed consent forms (ICFs).

BACKGROUND

Ethical principles of human research require that informed consent must be obtained from any subject who agrees to participate in a clinical trial. In order to obtain informed consent from the participant, an informed consent form (ICF) is created that discloses all relevant information about the research, ensures that the subject comprehends the information being provided, and voluntarily agrees (i.e. is not in any way coerced) to participate in the study. In order to achieve the objective of ensuring that the subject comprehends the information being provided, all ICFs must be presented to the patient in their native language. Consequently, translation of the ICF is a key step in launching any trial where linguistically diverse patient populations will be participating.

Although the informed consent form is a key document in any clinical trial, sponsors often fail to anticipate the requirements to translate the document or to monitor and effectively archive revisions to both the original and its corresponding translations. As a result, practical problems that can cause confusion or even delay the start of their trials are often encountered.

METHODS

A preliminary review of 2,506 archived informed consents was performed. This review revealed that the content of many informed consents created before 2010 appeared to be substantially different than the content of those created beginning in 2010. As a result, informed consents created prior to 2010 were excluded from our review, leaving a database of 1,767 informed consent documents created by 32 sponsors between 2010 and 2012 for further examination.

There were two purposes for analyzing this extensive database of documents. First, we sought to answer a common question posed by many sponsors. What is standard industry practice regarding the need to create both forward and back translations of ICFs and is it necessary? Second, we sought information about which languages sponsors most commonly require.

After completing the global analysis of the complete population of selected ICFs, we conducted a detailed analysis of the structure of a random sample of 78 of these informed consents across a group of 19 different sponsors. The analysis of each ICF selected involved a review of all information used to uniquely identify the informed consent and link it to a clinical trial protocol. This information is essential for legal purposes since sponsors are obligated to provide each patient with specific and accurate information describing how the trial will be conducted, the risks of participation in the trial, and outlining the patient's rights if they do choose to participate. However, the information that links an ICF to its protocol also has an important practical purpose in that it can be used by sponsors to efficiently ensure that translated versions of their ICFs match the original English version approved during IRB or ethics review. If used properly, this information can also play a significant role in reducing the total cost required to translate informed consent forms for their clinical trials while maintaining the consistency required in these documents.

Unique identification of each ICF is key to the management of these documents. Often times various versions have only subtle differences that are not obvious at first glance. Therefore, developing a coding method is essential. Our in-depth review focused on collecting several easily discernible factors needed to effectively manage and identify informed consent documents. The factors we analyzed were:

- The type of information contained in the header and footer of each document
- Whether or not the ICFs were templates that could be modified for use at any site or were site-specific versions
- The level of consistency of informed consents from a single sponsor across multiple studies
- Whether or not special California requirements were provided for when translations were requested

RESULTS

Database Review

Back Translations

As shown in **Table 1** below, 39% (683) of requests involved both forward and back translations, while 48% (848) did not. An additional 236 of the requests (13%) were for translations into English for which no forward translation was ordered at the same time. This appears to be explained by two factors. In some cases sponsors did not request back translations, but later came back with the request. In other cases, the sponsor seemed to be seeking a back translation of an ICF created by a site or another language service provider.

Table 1 – Frequency of Requests for Forward and Back translations of Informed Consents Among all Requesters from 2010 to 2012

Category	Back Translation Also Requested	No. of ICFs	% of Total No. of ICFs
No. of ICFs translated into a foreign language	No	848	48%
No. of ICFs translated into a foreign language (back translation only)	Yes	683	39%
No. of ICFs translated into English	No	236	13%
Total No. of ICFs		1,767	100%
Total No. of Sponsors		32	

Requests by Language Pair

Table 2 shows the distribution of requested translations by language pair. The review of our ICF database indicated that 27% (475) involved translation from English to Spanish for the US, making this the dominant language pair requested. A further 2% (34) were translations from US Spanish into English. The second most frequently requested language pair was English to French for Canada and back to English. These two language pairs appeared with equal frequency of 9% each, representing a total of 321 informed consents. The remaining 53% of all requests were for a variety of language pairs, with no clear pattern emerging.

Table 2 – Informed Consents by Language Pair Requested

Category	No. of ICFs	% of Total No. of ICFs
No. of ICFs translated into US Spanish	475	27%
No. of ICFs translated from US Spanish into English	34	2%
No. of ICFs translated into French for Canada	156	9%
No. of ICFs translated from French for Canada into English	165	9%
All other languages	937	53%
Total No. of ICFs	1,767	100%
Total No. of Sponsors	32	

In Depth Review of Sample of 78 ICFs

Requests by Language Pair

As shown in **Table 3**, the sample selected involved a majority of ICFs that had been translated into Spanish for the US (44 instruments, 56% of total sample). An additional 18% (14) of sampled ICFs were translated to French for use in Canada. The sample covered a total of 19 sponsors. However some of the ICFs (10%) had been created for the sponsor by a CRO or IRB.

Table 3 – Informed Consents by Language Pair Requested for Sample Selected for In-Depth Analysis

Category	No. of ICFs	% of Total No. of ICFs
No. of ICFs translated into US Spanish	44	56%
No. of ICFs translated from US Spanish into English	0	0%
No. of ICFs translated into French for Canada	14	18%
No. of ICFs translated from French for Canada into English	0	0%
All other languages	20	26%
Total No. of ICFs	78	100%
Total No. of Sponsors	19	

Requests by Identifying Characteristics

A total of 15 characteristics were identified as being potentially useful either in uniquely identifying a translated informed consent form and matching it to its corresponding English version or because they were important elements that could serve to reduce translation costs for the sponsor. The characteristics selected as well as the reasons they are important are shown in **Table 4** below.

Table 4 – Identifying and Cost Reduction Characteristics Commonly Found in ICFs

Identifying Characteristic	Reasons Identifying Characteristics are Important
Site Specific	Cost
Site Specific Protocol Used	Potential identification problem
Page numbers on each page	Ease in matching foreign language versions to original
Protocol Number	Unique identifier
Protocol Amendment Number	Unique Identifier
Protocol Amendment Date	Unique Identifier
Informed Consent Version Number	Unique Identifier
Informed Consent Version Date	Unique Identifier
IRB Approval	Unique Identifier
IRB Approval Date	Unique Identifier
Space for Patient Initials on each page	Legal
Space for Patient Initials Date Signed on each page	Legal
California mandated disclosure text	Legal/Cost efficiency since many trials are run in California
Space for Investigator to sign informed consent on signature page	Unique identifier. Also a legal requirement in some countries or required by some investigational sites.
Investigator name on each page	Unique Identifier

The frequency with which each of the 15 identifying characteristics appeared in the sample ICFs is shown in **Table 5**. The results of this analysis show that the **most common** characteristics seen across more than 50% of the 78 informed consents analyzed were:

- the existence of page numbers on every page
- the inclusion of the protocol number on each page
- the appearance of a site-specific protocol number (with or without the sponsor's protocol number) (for site-specific informed consents only)

The **most infrequently observed** characteristics were:

- space provided on each page for the date the patient initialed the consent
- existence of a protocol amendment number
- inclusion of California specific wording in template ICFs

It is worth noting that our review showed two frequently occurring problems with these documents. First, it was often difficult to discern whether a version number or date appearing on an ICF referred to the protocol or the informed consent document itself. Second, when investigational sites substituted their own site protocol number for the sponsor, it became impossible to track the informed consent to a specific sponsor's trial. For purposes of this study, situations such as these are classified as ambiguous in **Table 5**.

Table 5 – Occurrence of Identifying and Cost Reduction Characteristics Commonly Found in ICFs

Identifying Characteristic	Yes	% of Total	No	% of Total	Ambiguous	% of Total	Other	% of Total
Site Specific	49	63%	29	37%	N/A	-	-	-
Site Specific Protocol Used	39	79%	10	21%	N/A	-	-	-
Page numbers on each page	68	87%	10	13%	N/A	-	-	-
Protocol Number	59	76%	11	14%	4	5%	4[a]	5%
Protocol Amendment Number	7	9%	67	85%	2	3%	2	3%
Protocol Amendment Date	10	13%	54	69%	14	18%	-	-
Informed Consent Version Number	24	31%	34	43%	20	26%	-	-
Informed Consent Version Date	33	44%	11	14%	34	44%	-	-
IRB Approval	26	33%	50	64%	N/A	-	2[b]	3%
IRB Approval Date	25	33%	51	65%	N/A	-	2	3%
Space for Patient Initials on each page	36	46%	42	54%	N/A	-	-	-
Space for Patient Initials Date Signed on each page	9	12%	69	88%	N/A	-	-	-
California mandated disclosure text	15	19%	1[c]	1%	N/A	-	58	74%
Space for Investigator to sign informed consent on signature page	24	31%	54	69%	N/A	-	-	-
Investigator name on each page	16	21%	62	79%	N/A	-	-	-

[a] Two ICFs were inconsistent and combined the drug substance code name with the protocol number; Two ICFs referenced EUDRACT numbers
[b] Two ICFs were stamped by the IRB but there had been no provision by the sponsor to include IRB approval information.
[c] Four ICFs contained the mandatory California wording but were in the wrong site type (14 pt. mandated in California).

DISCUSSION

In analyzing the result of our database review of ICFs, several trends became obvious. With reference to sponsors' query about the need for both forward and back translations, we found that there was no clear agreement on whether or not both forward and back translations were necessary for these documents. Our review showed that only 39% of requesters asked for both a forward and back translation when their initial order was placed. Even within companies that have policies that require that they perform both forward and back translations of all ICFs, there were many instances in which this policy appears not to have been followed. Both the FDA and the EMA are also unclear with regard to whether or not a back translation of an ICF is required.[1,2] To meet the requirements of 21 CFR 50.20, the non-English speaker must be provided with a translated consent document that is accurate. The agency does not specify how accuracy is to be determined. EMA does not discuss translation requirements.

The analysis also revealed that all sponsors included some identifying information that would link the ICF to a specific protocol. However, the type and display of that information varied widely. Our review of the factors listed in **Table 5** indicated that while each sponsor may have standards for creating informed consent documents, these standards are only loosely followed. In many cases, multiple formats were issued by the same sponsor. On occasion divergent formats resulted from the fact that a CRO or IRB had provided the ICF to the sponsor and used their own template rather than the template normally used by the sponsor. In other cases, there appeared to be no clear reason for the differences other than that they were created by different sponsor sites which may have varying practices.

The lack of consistent standards for mandatory identifying information on ICFs leads to numerous problems when the document must be translated into other languages. Primary among those problems is the inability to easily match a translated informed consent with its translation – a situation that can result in different patients receiving different versions of the informed consent document should multiple versions be allowed to circulate. While it seems obvious that characteristics such as protocol number, ICF version number and IRB approval information should be included in an ICF template, many of these elements were commonly omitted from or ambiguously labeled in the ICFs we analyzed. Since ICFs often go through revisions due to protocol changes or specific site requirements, failure to include this information makes it extremely difficult to match foreign language versions to original English versions if information is missing or displayed in an unclear way. Given that differences between versions may be small and difficult to detect by the non-native speakers who may be handling and administering them, the opportunity for confusion is abundant.

A second important reason for including key identifying information relates to the cost of translating these documents. A savvy LSP will use this information to track the ICFs provided by a sponsor. Creating a system that can track these versions and determine exactly what changes have been made can reduce the amount of new translation required and, therefore, be an effective method of reducing the sponsor's overall translation costs. For example, during our review we noted that one sponsor listed their protocol number on an ICF using their usual coding system. In another ICF for the same study, the sponsor included the study drug code as a prefix. Unless they had seen many other ICFs from this sponsor, even the most effective LSP would likely have identified the two ICFs as belonging to different studies and not been able to locate the previously translated text. This situation could easily lead to the same ICF being translated twice and being translated differently. The result would be that different patients could unnecessarily receive different translations of the same ICF while the sponsor would have doubled its cost.

Best Practices for ICF Management

Best practices for translation of ICFs dictate specific responsibilities on the parts of both the sponsor and the LSP.

Sponsor Responsibilities

In order to ensure the efficient handling of ICFs and their translations, sponsors have several key responsibilities. Among them are the following:

- Designing an informed consent with unique identifiers that link it to its protocol (and amendment), to its IRB/ethics approval, and to an investigational site.
- Setting policy regarding whether or not both forward and back translations will be performed
- Selecting a single LSP to perform all translations for a single protocol
- Ensuring that the selected LSP understands the protocol and ICF versioning conventions

Charts 1-3 show examples of an effective way to display identifying information on an informed consent.

Chart 1 shows a sample header that provides all information related to the protocol as well as page numbering. This header should appear on all pages of the consent form.

Chart 1: Sample Informed Consent Header

Sponsor's Protocol # with Amendment # if applicable *Protocol Amendment Date*		*Page X of Y*

The recommended sample cover page should contain a table as shown in **Chart 2**. This table provides general information and an easy mechanism for updating it for specific investigational sites.

Chart 2: Sample Information to be Provided on Cover Page of ICF

Study Title: _____
Sponsor: _____
Protocol Number: _____
Principal Investigator: _____
Telephone: _____
Address: _____
Subject ID Number: _____

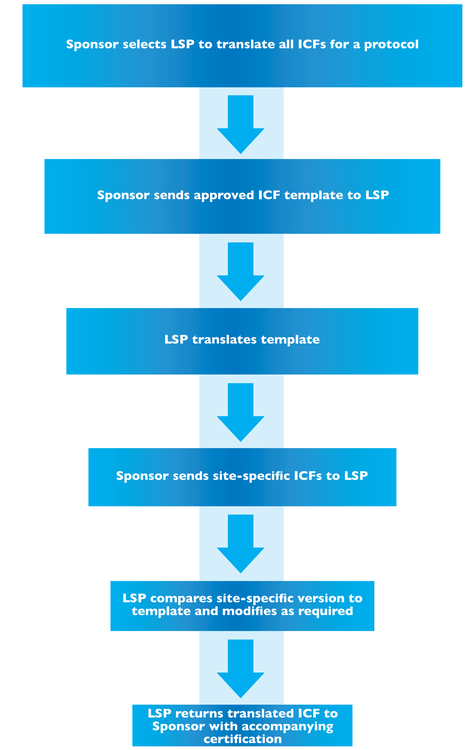
Chart 3 shows a sample footer that should appear on all pages of the ICF. This footer provides all ICF versioning and IRB information. Note that this format allows for site specific and patient specific information that might otherwise be made by an investigational site.

Chart 3: Sample Informed Consent Footer

Last Name of Principal Investigator	IRB Name, IRB Version, IRB Approval Date	Legally Authorized Representative/Subject's Initials _____
	Sponsor Version Name (Main, PG, PK, etc.), Sponsor Version# Sponsor Version Date	Date Signed _____

When all elements found in **Charts 1-3** are combined into a single ICF, most regulatory requirements are met in both the US and Canada. An added benefit of using this model as a standard is that investigational sites will make fewer revisions and the LSP will be better able to track study ICFs as they change over time. Both outcomes will ultimately reduce the final cost for translation of these documents if the sponsor works closely with a single LSP.

When the sponsor and LSP work as a coordinated team, the workflow will look like this:



LSP Responsibilities

LSPs that handle all of the informed consents for a single protocol are responsible for:

- Obtaining adequate information from the sponsor about sponsor's protocol and ICF naming conventions.
- Creating an efficient system for tracking informed consents by protocol, investigator and type of ICF (main, PK, PG, etc.)
- Providing consistent translations across that protocol.
- When a back translation is requested, performing a reconciliation between the source document and the back translation and resolving any discrepancies prior to finalizing forward translation.
- Creating certifications that contain all key identifying information found in Charts 1-3 above so that the translations can be easily matched and archived.
- Determining the most cost-effective way to revise ICFs while maintaining consistency between versions.

CONCLUSIONS

Our review of an extensive number of informed consent documents across 32 sponsors as well as our detailed review across 19 sponsors showed no clear agreement on what constituted standard industry practice for these documents and their corresponding translations. Sponsors use numerous formats for their consent forms and often omit information necessary to track the evolution of the consent form, to associate it with a specific protocol, or to match it with its translated versions. In light of the legal and ethical requirements that patients participating in clinical trials be fully informed of the inherent risks of participation, informed consents and their translations need to be carefully managed in order to avoid confusion in their administration. We recommend that sponsors create and enforce the use of a standard informed consent template to be used by all internal and outsourced clinical teams in order to reduce unnecessary confusion and risk. Our investigation shows that creating such a standard will have the beneficial effects of improving patient safety and reducing the overall cost of translating these important instruments.

VOCABULARY

Forward Translation: Conversion of a document from one language (source language) to another language (target language).
Back Translation: A useful review tool, a translation of a translation, from the target language into the source language.
Reconciliation: Process by which a translation is checked against the source document to verify that all concepts were translated as they were intended in the original.

REFERENCES

1. http://www.fda.gov/RegulatoryInformation/Guidances/ucm126431.htm, March 19, 2012.
2. www.ema.europa.eu/pdfs/human/ich/013595en.pdf, March 19, 2012.

CORPORATE TRANSLATIONS

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