Reduced quality of life impacts knowledge and type of informed consent in rheumatoid arthritis patients

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Abstract

Objective

Informed consent (IC) is an ethical process required in human subject research. Primary objective was to determine factors associated to poor knowledge of IC content (PK) in patients from an early rheumatoid arthritis cohort.

Methods

The cohort initiated in 2004, had assistant and research purposes (NCT03389711). At inclusion, each patient selected 1 of 4 options of the IC form; options ranged from broad consent (patient's data could be used for research) to patient denied to have his/her data used. Once enrolled, patients had regular assessments.
Up to May 2017, the cohort had 146 patients with (median, range) follow-up of 8.8 years, (4.3-11.9) and 143 agreed to participate in a cross-sectional study; patients had scheduled rheumatic evaluations; additionally, a social worker applied a questionnaire that addressed objective described. PK was established by the borderline performance method. Multiple regression models were applied to investigate factors associated to PK.

Results

At cohort inclusion, patients were primarily middle-aged (38.3±13.1 years) females (88.9%), with high disease activity (DAS28: 5.8 [4.6-6.8)] and poor quality of life (SF-36: 42 [29-59]). All the patients gave broad IC.
At study entry, 35-41.3% of them had PK; longer follow-up and lower SF-36 scores at cohort inclusion, were associated to PK. In addition, 79.7% of the patients had DAS28-remission and 67.1% had SF-36 scores within normal range; interestingly, only 49% of the patients considered broad re-consent and these patients had poorer SF-36 emotional subscore than their counterpart (79±23 vs. 87±1, p=0.02).

Conclusion

Poor quality of life impacts the autonomy of RA patients.

Key words
informed consent, quality of life, rheumatoid arthritis

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Received on February 16, 2018; accepted in revised form on April 24, 2018.

Competing interests: none declared.

Introduction

Rheumatoid arthritis (RA) is a chronic and potentially disabling disease occurring worldwide, that can affect all the health-related-quality-of-life (HRQoL) patient's dimensions (1); these refer to the impact of health/disease on individual's well-being, in the context of their larger financial, social and political environment, not all of which may be improved when the underlying disease ameliorates (2). Primary objectives of RA treatment are to improve and to maintain physical and social functioning (3); OMERACT, the international consensus effort that assesses outcomes measures in rheumatology, has recommended the incorporation of generic measures of HRQoL, in addition to disease-specific measures, when assessing RA patients (4). The 36 item Medical Outcome Study Short-Form survey (SF-36) is a generic instrument that assesses HRQoL, and the most widely used in RA patients (5).

Longitudinal cohorts are an excellent source of information on the causes and outcomes of many rheumatologic diseases, including RA. They contribute to our knowledge regarding the relative efficacy of specific therapeutic interventions that are impossible or impractical to assess using randomised controlled trials (6). Such cohorts are clinical healthcare instruments that provide a basis for medical research (6, 7).

In 2004, at the "Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán" (INCMyN-SZ), we began assembling an incidental cohort of patients with recent-onset RA for assistant and research purposes. The cohort is dynamic, and the patients are followed until their death or eventual loss to follow-up (8). The cohort was approved by the Research Ethics Committee (Reference: IRE 274). All patients signed an informed consent (IC) form on inclusion in the cohort whereby they could choose between four mutually exclusive options: 1) The patient authorises the use of his/her information for scientific research related to RA, 2) for scientific research related or not to RA (that is, including other diseases), 3) for either type of research if the patient is contacted in advance and accept, and 4) the patient refuses to authorise the use of his/her data for research purposes. Consent for biologics samples is also obtained.

IC is a process that encompasses all actions that promote adequate communication between physician and patient (9) and is based on the principle of autonomy (of the patient) with respect to making free and responsible decisions regarding his/her health (10). Because of the legal and ethical implications of IC, the IC form is often written in legal prose (11) and difficult to understand for many patients, who in addition may find themselves in a vulnerable state because of their illness (12, 13). Similar to any dynamic process, IC is subject to change. In longitudinal research projects, the validity of IC has been questioned because patients a priori cannot agree to future use of their data and/or the samples they provide when they sign the IC form (14). In these cases, re-consent may be an approach that helps improve communication (15).

Patients with recent-onset RA who accept to participate in a cohort for assistance and research purposes are vulnerable because of the diagnosis of the disease itself. This vulnerability may lead them to sign the IC form thinking it will enable them to receive medical care sooner. Longitudinal cohorts involve long-term patient follow-up, during which clinical improvement frequently occurs (8), without any regulations requiring researchers to revisit the topic of patient participation in research, an area that differs from medical care.

The objective of this cross-sectional study was to determine the degree of knowledge regarding the content of their IC among a cohort of patients with recent-onset RA and to associate that knowledge level with sociodemographic characteristics (*e.g.* patient age and education), disease activity, patient-reported outcomes and follow-up time. As a secondary objective, the value the patients place on their IC and their preferences regarding re-consent were assessed.

Materials and methods

Study population and intervention maneuver

All the patients of the cohort who were actively followed and had at least six

months of cohort follow-up (n=146) were invited to participate in the study. A total of 143 agreed. A female social worker administered a questionnaire during a personal and structured interview (see Supplementary information 1). The social worker was involved in the cohort design and follow-up, and is a candidate to a PhD in Health Sciences. In addition, on the same day as the interview, the patients were subjected to a complete rheumatologic evaluation, as described in the literature (8).

Development of the evaluation instrument (Supplementary information 1)

Three researchers familiar with the cohort developed a questionnaire, which included four dimensions: 1) Degree/level of knowledge regarding the content of one's IC, 2) the value placed by the patient on his/her IC, 3) patient´s preferences regarding re-consent and 4) patient's knowledge regarding the principle of autonomy. We report the results for dimensions 1, 2 and 3 according to the described objective.

To integrate dimension 1, the researchers reviewed the IC form provided to each patient on inclusion in the cohort and individually identified the issues they considered the patient should comprehend. Issues with at least 80% agreement were retained. Dimension 1 included the following:

- A question that assessed whether the patient remembered having signed the IC form on inclusion in the cohort, and a patient self-evaluation on how the patient rated his/her knowledge regarding the IC (Likert scale: poor, average and superior); and,
- Eleven consecutive items that evaluated the dimension "Level/degree of knowledge regarding one's IC" in the form of true (T) or false (F) questions.

The dimension "Value the patient placed on his/her IC" (*i.e.* did the patient retain the IC form?; did the patient share the information that he/she had provided his/her IC?; does the patient remember where his/her IC form is?) was addressed using six questions: three true (T) or false (F) questions, two multiple-choice questions with four possible answers each and one open-ended question.

Dimension 3 on preferences regarding re-consent included three questions: one true (T) or false (F) question, one multiple-choice question with four possible answers and one open-ended question.

Pilot test

A pilot test was performed using a convenience sample of 20 consecutive patients. The phrasing of the questions and the survey administration time were assessed. The characteristics of these patients displayed no significant difference from those of the cohort population (data not shown).

Questionnaire scoring

For the dimension "Level/degree of knowledge regarding one's IC", two scores were integrated as follows. The first score (Overall Knowledge) considered items 3 to 13 (Supplementary information 1). For each correct answer, one point was awarded, and the average was calculated to a decimal scale. This exercise was repeated considering only items 4, 7, 8, 9, 11 and 13 (Specific knowledge). The remaining items were discarded (identified with * in Supplementary information 1) because they contained information explained during the patient's follow-up in the cohort, that was not necessarily specified during the visit in which patient was admitted to the cohort.

Immediately after administering the survey, the surveyor determined the degree of knowledge regarding one's IC (Likert scale: poor, average and superior). This evaluation was used to establish the cut-off point for defining the degree of knowledge regarding IC as poor.

The dimensions "Value the patient placed on his/her IC" (items 15-18 and 20) and "Preferences regarding re-consent" (items 21-23) were not scored.

Statistical analysis

The sample size was calculated using the formula for cross-sectional studies to estimate a prevalence. Based on the pilot study results, we assumed a 40% prevalence of poor knowledge in the 146 RA patients with active follow-up, a level of confidence of 95% and a precision of 0.10, resulting in a sample size of 94 patients. However, in order to address potential associations of patients and disease characteristics with poor knowledge, all the patients actively followed in the cohort were invited to participate. In addition, due to the ethical implications of exploring re-consent, it was deemed convenient to extend the invitation to all the patients.

The descriptive statistical analysis was expressed as percentage, mean ± standard deviation (M±SD) and median (quartile 25 [Q25] – quartile 75 [Q75]). Poor knowledge was defined based on a cut-off point established using the borderline performance method (16). The questionnaires of the patients scored by the rater as average (or borderline) for the dimension "Degree/level of knowledge regarding one's IC" were selected, and the mean score of each dimension was calculated. Any value lower than the mean was considered poor knowledge.

SF-36 norm was considered if ≥80 on a scale from 0 to 100. The cut-off was derived from data obtained from a healthy Mexican population (17).

The variables of interest were compared between the groups of patients for overall and specific knowledge regarding their IC, both poor and sufficient, using the χ^2 and Mann Whitney U-tests.

Logistic multiple regression models were used to establish the associations between the possible explanatory variables and the degree/level of knowledge regarding the content of one's IC. The selection of the variables to be included was based on their statistical significance in the bivariate analysis ($p \leq 0.11$). In addition, the number of variables to be included was established a priori in order to avoid over-fitting of the models. Variables considered were: baseline sociodemographics, baseline disease-associated outcomes, baseline patient-reported-outcomes and follow-up in the cohort (up to interview). Finally, comorbid conditions were included as confounder variables. Collinearity between variables was ruled-out. The construct validity of the instrument in assessing the degree/level of knowledge regarding the content of

one's IC was established by comparing the mean scores of the instrument between patients with average vs. poor knowledge (Student's *t*-test) and by comparing the distribution of patients classified according to the Likert scale as possessing poor, average and superior knowledge between the quartiles of the scores of the instrument assessing this dimension (χ^2 test).

A two-tailed *p*-value ≤0.05 was considered significant. All tests were performed using the statistical package SPSS v. 18.

Ethical considerations

The study was approved by the Research Ethics Committee (REC) of the INCMyN-SZ (Reference 2199) and by the REC of the School of Medicine, "Universidad Panamericana" (Reference E1702). Both RECs granted a waiver to request only verbal consent (18). Good practice guidelines for medical research were followed during the study.

Results

Patients' characteristics

At cohort inclusion, patients were primarily women (127 [88.9%]) with medium-low socioeconomic status (128 [89.5%]). The mean (±SD) age was 38.3 (± 13.1) years, and the mean education was 11.4 (± 3.8) years. Most patients exhibited a rheumatoid factor (122 [85.3%]) and antibodies against citrullinated proteins (128 [89.5%], one missing data) and a Disease Activity Score (DAS28) (19) of 5.8 (4.6-6.8) (median, interquartile range). The patients reported a visual analogue scale (VAS) of pain of 50 mm (28-73), an overall VAS of 53 mm (30–76), significant disability as defined by the Health Assessment Questionnaire (HAQ) (20) of 1.4 (0.6-2) and a poor quality of life score as defined by SF-36 (5, 17, 21) of 42 (29-59).

At the time the questionnaire was administered, the mean (± SD) patient age was 46.9 (± 13.6) years, and the median (interquartile range) cohort follow-up was 8.8 (4.3–11.9) years. Most patients were in remission according to the DAS28 (114 [79.7%]), 115 patients (80.4%) showed no disability and 96 patients (67.1%) had SF-36 scores within normal range.

Table I. Comparison of characteristics at cohort entry between patients with poor *vs*. average level of specific knowledge regarding one's IC (primary objective).

Variables	Poor knowledge	Average knowledge	*p*-value
Sociodemographic			
Female, n. (%)	54 (91.5)	73 (86.9)	0.433
Age in years[1]	37.2± 13.2	39.1 ± 13.1	0.384
Education in years[1]	10.7± 3.5	12 ± 3.9	**0.034**
Medium-low socioeconomic status, n. (%)	56 (94.9)	72 (85.7)	**0.099**
Disease-specific			
ESR, mm/H[2]	21 (13-45)	19 (9-39)	0.351
DAS28 (0-10)[2]	5.9 (4.6-6.8)	5.8 (4.5-6.8)	0.492
n. of inflamed joints (0-28)[2]	13 (7-18)	13 (8-17)	0.908
Patient outcomes			
Pain VAS (0-100)[2]	54 (28-73)	49 (33-73)	0.931
Overall VAS (0-100)[2]	57 (33-86)	52 (28-76)	0.391
HAQ (0-3)[2]	1.5 (0.5-2.3)	1.3 (0.8-2)	0.534
SF-36 (0-100)[2]	33 (22.4-57.5)	46 (33.6-59.9)	**0.027**

[1] (mean ± SD); [2] median (interquartile range).
IC: informed consent; ESR: erythrocyte sedimentation rate; DAS28: disease activity score; VAS: visual analogue scale; HAQ: Health Assessment Questionnaire, SF-36: Short-Form 36; n: number.

Table II. Variables associated with average overall and specific knowledge regarding one's IC.

	Variables	OR	95% CI	*p*-value	R^2
Overall knowledge regarding IC	Follow-up time (years)	0.89	0.81-0.97	0.011	0.065
Specific knowledge regarding IC	SF-36 score	1.02	1.001-1.04	0.035	0.043

OR: odds ratio; CI: confidence interval; IC: informed consent; R^2: squared correlation coefficient.

Table III. Concurrent validity between the degree of overall (O) and specific (S) knowledge regarding one's IC, based on the Likert scale and a questionnaire assessing the corresponding dimension of the survey.

	First quartile 0-2.5		Second quartile 2.6-5		Third quartile 5.1-7.5		Fourth quartile 7.6-10	
	O	S	O	S	O	S	O	S
Poor knowledge	6	8	3	4	3	0	3	3
Average knowledge	0	2	8	24	23	9	20	16
Superior knowledge	0	1	2	20	29	18	46	38

Level of knowledge regarding one's IC (primary objective)

The rater assessed that 51 patients (35.7%) had intermediate knowledge, according to the Likert scale. The mean overall and specific scores for the dimension "Degree/level of knowledge regarding one's IC" of these 51 patients were 7.23 and 6.38, respectively. Poor overall knowledge was defined as a score ranging from 0 to 7.22 points and poor specific knowledge as a score ranging from 0 to 6.37 points. Fifty patients (35%) had poor overall knowledge, and 59 (41.3%) had poor specific knowledge.

Variables associated with a poor level of knowledge regarding one's IC (primary objective)

Table I shows the comparison of the following characteristics at cohort entry, between patients with a Poor *versus* Average specific knowledge regarding one's IC: Sociodemographic characteristics, disease specific and patient-reported outcomes. The results for the level of overall knowledge regarding one's IC were similar and are not shown. The patients with poor specific knowledge had a lower education level, more frequently possessed medium-low socioeconomic status and had worse

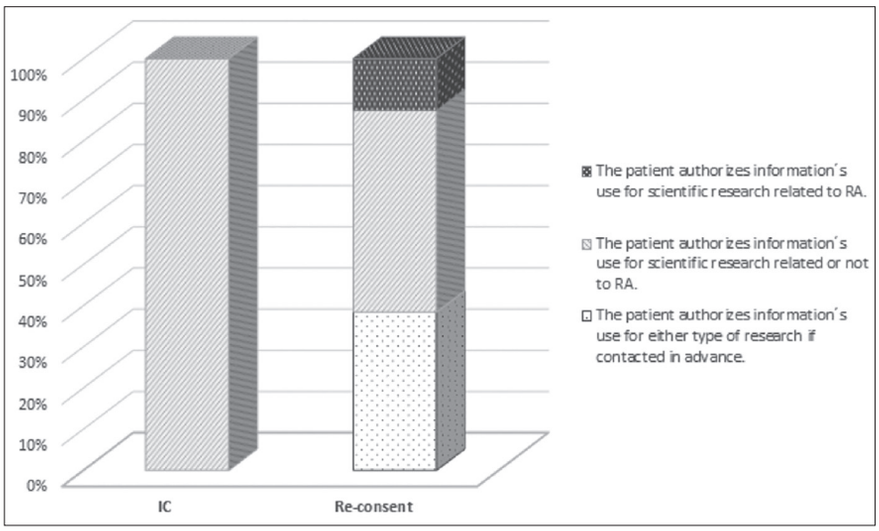

Fig. 1. Mutually exclusive options of the IC form provided to patients at cohort inclusion, and at re-consent. Figure shows % of patients who selected a particular IC option at cohort inclusion (first bar), and at study entry, when re-consent preferences were explored (second bar). Options were as follows:
1. Patient's data could be used for research purposes only related to RA;
2. Patient's data could be used for research purposes (without restrictions);
3. Patient's data could be used for research purposes (related or not to RA), but the patient needs to be previously notified.

HRQoL according to the SF-36. Treatment and comorbidities exhibited no significant difference (data not shown). Finally, years of follow-up tend to be longer in the patients with poor specific knowledge: 9.3 (6.3-11.9) *vs*. 8.8 (3.6-11.9) years, p=0.107.

The following variables were selected for inclusion in the different multiple regression models: Years of education, SF-36 score (*i.e*. HRQoL), low socioeconomic status and cohort follow-up time. The logistic multiple regression analysis was repeated for overall and specific knowledge (Table II). A longer follow-up time in the cohort was associated with a lower probability of average overall knowledge score, whereas a better quality of life on inclusion in the cohort was associated with a higher probability of average specific knowledge score.

Value placed on one's IC

At the time of the survey, most patients (91 [63.6%]) did not remember the IC-form option that they authorised on their inclusion in the cohort. Of the 52 remaining patients, only 8 patients (15.4%) adequately recalled the option they selected at the time.

Most patients had shared the information that they had provided their IC (105 patients [73.4%]), nearly all (94.3%) with a family member.

Last, 79 patients (55.2%) retained the IC form (original instead of a copy is required in México), 6 (4.2%) did otherwise, 38 (26.6%) had lost it, and 20 patients (14%) stated that they had not received it.

Preferences on re-consent

On inclusion in the cohort, all patients selected option 2 (for scientific research related or not to RA, without the need to contact the patient). At the time of the survey, only 70 patients (49%) chose their previously selected option, 55 (38.5%) chose option 3 (research related or not to RA if the patient is contacted to confirm his/her authorisation), and 18 patients (12.6%) chose option 1 (only for research on RA) (Fig. 1).

The patients were divided into two groups. The first consisted of those who chose a broader re-consent (option 2) when updating their IC form (n=70). The second consisted of those who chose a more restricted re-consent (options 1 and 3, n=73). Interestingly, the patients who selected a broader re-consent had worse HRQoL than those who selected a more restricted re-consent: mean (±SD) SF-36, 79±23 *vs*. 87±10, p=0.02.

Finally, 32 patients (22.4%) selected six months later as the ideal time to re-discuss their participation/inclusion in the cohort, 82 patients (57.3%) chose 12 months, and 13 patients (9.1%) chose 24 months. The other patients expressed no preference.

Validity and concordance of the questionnaire on the degree/level of knowledge regarding one's IC

The patients with average or superior overall and specific knowledge according to the Likert scale had higher (mean ± SD) scores for the dimensions that corresponded to their instruments than their counterparts: 3.9±3.5 *vs*. 7.6±1.8 ($p \leq 0.0001$) and 3.0±3.3 *vs*. 6.8±2.3 ($p \leq 0.0001$), respectively.

Table III shows that a higher number of patients with average and superior knowledge were concentrated in the quartiles with the highest scores for the dimension "Degree/level of knowledge regarding one's IC" ($p \leq 0.0001$).

Discussion

This longitudinal study was conducted on a cohort of patients with recent-onset RA for assitant and research purposes. The cohort included several methodological recommendations to ensure data quality (6). A questionnaire, whose construct validity was examined, was administered to all patients. Its results were analysed using a robust method (16). The questionnaire was administered by a social worker trained in research to avoid biases and attending-physician effects (22). Relevantly, the study adopted a distinctly ethical approach to the context of rheumatology, an area in which several authors have noted a lack of (ethical) discourse (23-26).

The primary objective of the study was to determine the patients' level of knowledge regarding their IC. This objective was consistent with the philosophical perspective of Beauchamp and Childress on IC, which they regard as a continuous process between the physician and the patient (27) in contrast to its legal perspective, which is (over)emphasised by the act of signing a document. We found that slightly more than one third of our patients had poor knowledge regarding the content of their IC.

The literature reports similar results for both clinical (28) and research (29, 30) contexts, albeit outside the context of rheumatology field. In addition, in this medical specialty, certain researchers have suggested that signing the IC form before each clinical procedure not only does not guarantee correct patient information but may also transform the medical intervention into a bureaucratic act, thus distancing it from the Hippocratic ideal, which is based on a relationship of trust between the patient and the attending physician (15).

We found that worse HRQoL on inclusion in the cohort was associated with poor knowledge regarding one's IC in subsequent years. Interestingly, the patients who at the time of the survey had worse HRQoL (as per SF36 emotional subscore) opted for a broader re-consent option. That is, they did not place restrictions on the use of their data for research. Last, and as previously described, we observed that all patients selected a broad IC option on admission to the cohort, when they first received the RA diagnosis and had high disease activity, substantial disability and poor HRQoL. However, years later, when the clinical situation and the outcomes reported by the patient had markedly improved, more than half (51%) chose a more restricted re-consent option. Ideally, the provision of IC requires that the patient analyse the clinical situation, understand the consequences of the proposed diagnosis and treatment (including alternatives) and the future implications of the treatment as well as integrate all the information into a decision (31). This process should occur within an ethical framework of respect for patient autonomy, whose possibility may be questionable for certain chronic diseases (32). In addition, one should note that in research and clinical practice, the ideal procedure may be compromised in the name of meeting specific legal requirements (11) and when considering patient vulnerability.

Vulnerability is an anthropological dimension of human beings and intrinsic to human life (12). It is defined as the (relative or absolute) inability to protect one's own interests (33, 34) and may be fundamentally classified into two types: extrinsic (due to external circumstances, such as low socioeconomic status, lack of education and resources or lack of access to healthcare) and intrinsic (determined by the characteristics of the individual, such as suffering from serious disease or psychological problems) (33). The patients included in this study exhibited both types of vulnerability. Most were of medium-low socioeconomic status (8), had limited education (8) and were recently diagnosed with RA, a chronic, potentially progressive disease that changes the lives of affected patients (35) and their relatives, all of which factors raise specific ethical issues (13, 36). Additionally, the patients in the cohort were seeking health care while playing a role in research; the World Medical Association has identified such patients as particularly vulnerable (30). It should be noted that a patient-reported outcome, *i.e.* (worse) HRQoL evaluated by a robust and widely used instrument in RA (SF-36) (3, 37), was associated with poor knowledge and a broader (re)consent; however, although a high and significant correlation was identified between the SF-36 and the DAS28 scores on inclusion in the cohort (rho=0.88, $p \leq 0.0001$), other measures considered as more objective in determining the disease activity status were not. In the literature, the impact of specific disease activity statutes (such as remission) on HRQoL has also been variable (38). Importantly, the SF-36 is an instrument that assesses the physical, psychological (or emotional) and social impact of RA and has been recommended for inclusion in patient evaluation as a measure of (self-) reported quality of life (4).

A notable result is that the patients apparently placed little value on their IC. Most could neither remember the option they had selected nor retain the copy of the form provided to them. Allen *et al.* (29) reported similar data, on patients who were even unable to remember having provided a blood sample. In our study, the time elapsed between signing the IC form and administering the questionnaires was substantial. In fact, the follow-up time was the only variable associated with average overall (but not specific) knowledge. However, given the cohort's prospective character, the long-term retention of biologic samples and the importance of the bioethical debate regarding withdrawing IC, the ability to remember key aspects of the research is particularly important (29). In its absence, we should use instruments to minimise bias.

The study has limitations. For one, it was conducted at a single centre and on a population with specific characteristics (39), which limits the generalisation of the results. In addition, the questionnaire on the level of knowledge regarding one's IC content was not formally validated although an exercise was conducted to establish its construct validity. The study was conducted on an observational cohort and therefore has the limitations of such cohorts, particularly follow-up losses and lack of standardisation and control with respect to certain variables and outcomes (7).

Today, the law, medical ethics and society demand that physicians incorporate the current ethical discourse into their practice. Paradoxically, only a minority of rheumatologists consider that the ethical literature on this matter is useful in daily practice (23, 26). In this study, we found that worse HRQoL on inclusion in the medical care and research cohort was associated with poorer knowledge regarding the IC content. Complementarily, patients who chose a broader IC were rated worse. We propose that in similar clinical contexts, re-consent, as a continuous instrument of communication between the physician and the patient, may help increase respect for patient autonomy over time. This proposal has been previously described although it has not been established when or based on what aspects to apply it (15). For patients diagnosed with RA (and likely any chronic disease that affects patient quality of life), we propose that the re-consent process be applied when adequate control of the disease is achieved and when the patient perceives this fact. Despite nearly two decades of debate, there is no consensus on the conceptual level of the IC model that best enables us to reduce the tension between patient and research interests (40). The "broad IC" model has been adopted by several biobanks and can be

incorporated in clinical contexts, such as the one described (41, 42). In addition, it has been shown that although subjects have a limited understanding of the character of the research, the IC process provides them some degree of control and self-determination, both of which are of substantial value to those involved (29).

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