

# Psychological Processes Experienced by Patients with Dilated Cardiomyopathy Participating in a Clinical Study: a qualitative study

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**Keyword** ; clinical study participation, psychological process, therapeutic misconception, qualitative study

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**Abstract** ; Background: Dilated cardiomyopathy (DCM) is a progressive disease of the heart muscle. Standard treatment mainly comprises of treating the symptoms of heart failure, so the development of effective therapies is urgently required. Patients with an intractable disease such as DCM are seeking new treatments for clinical studies. Some patients may confuse the research process for treatment, and therefore this misconception could result in an ethical problem of participation. In order to solve the therapeutic misconception, it is important to understand the patients psychological state, but there are few preceding studies. This study aimed to reveal the psychological processes in DCM patients by examining their personal experiences of clinical studies.

Methods: In total 11 DCM patients who visited the Kitasato Institute Hospital of Kitasato University for follow-up examination of the clinical study on immunoadsorption therapy from April 2011 through May 2012 were participating in this study. They participated in semi-structured, open-ended and in-depth interviews that surveyed their psychological process with clinical study participation. Patients' narratives were recorded and interview data was categorized using a qualitative analysis method.

Result: A total of 19 concepts were generated and grouped into categories. Patients have high expectations regarding clinical study participation, not only for the experimental treatment but also with respect to medical staff involved in the clinical study. Clinical studies strongly impact the awareness of participants towards treatment.

Conclusion: DCM patients had strong expectations about participating in this Clinical study. In order to solve the therapeutic misconception, it is important to understand the patients psychological state. So that we can work towards supporting them in their intractable diseases. This study may be informative the importance to understand the psychological statement of the intractable disease patients.

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## Introduction

Patients with intractable disease such as dilated cardiomyopathy (DCM) are seeking new treatments for clinical studies. On the other hand, the therapeutic misconception is an ethical problem. In order to conduct clinical research ethically, it is important to understand the participant's psychology for the clinical studies. The present study aimed to reveal the psychological processes in DCM patients by examining their experiences of clinical studies. DCM is a condition characterized by poor prognosis, marked expansion of the cardiac lumen, and advanced contractile dysfunction, resulting in severe congestive heart failure and refractory arrhythmia. Standard treatment mainly comprises treating the symptoms of heart failure and the prevention of further disease progression<sup>1)</sup>. As such, development of effective therapies is urgently required and potential causes must be elucidated. Currently, clinical studies on immunoabsorption therapy<sup>2, 3)</sup> and stem cell therapy<sup>4)</sup> are ongoing as advanced treatments for DCM.

Research interests in current medical development have shifted toward studies of intractable diseases, in consideration of the awareness of unmet medical needs. Clinical studies on intractable diseases are thus of increasing importance, even for those who conduct such studies. Among both participants and researchers, the demand for clinical studies of intractable diseases is high, and the number of conducted studies has been on the rise<sup>5)</sup> and is expected to increase further in the future.

Previous reports have demonstrated that the mental health of patients who

participate in clinical studies is impacted by this experience<sup>6, 7, 8)</sup>. When performing a clinical study involving patients with intractable diseases, such as those with DCM (which imposes a high therapeutic burden), the physical and psychological impact on these patients must be considered, more so than in general clinical studies. Despite this, very few studies have examined the psychological impact on patients. Among the few qualitative studies focused on the psychological processes of clinical study participants with intractable diseases is a study by Kohara et al., which examined the decision-making process experienced by cancer patients concerning participation in a phase I clinical study<sup>6)</sup>.

In the present study, we focused on psychological processes in patients with DCM, an intractable disease, by examining their experiences with clinical study participation. The results of this study should help provide psychological support to patients with intractable diseases and it's also useful for medical professionals to understand a patient.

## Methods

### *Patients and Recruitment*

DCM patients who visited the Kitasato Institute Hospital of Kitasato University for follow-up examination of the clinical study on immunoabsorption therapy from April 2011 through May 2012 were included in this study. The criteria of this clinical study were as follows: (1) diagnosis of DCM, (2) grade  $\geq 3$  subjective symptoms of heart failure according to the New York Heart Association functional classification, (3) left ventricular ejection fraction of  $\leq 35\%$ , (4)

receiving optimal treatment for heart failure with no improvement in medical condition for more than three months, and (5) age  $\geq 18$  years.

### *Procedures*

An interview survey was conducted at the time when immunoabsorption therapy was completed, i.e., the main part of the clinical study, when the participants visited our hospital for follow-up examination. Semi-structured interviews led participants to talk about events related to DCM as well as their psychological experience from the time when they noticed symptoms up to the present day. The semi-structured interview method used for data collection is based on an approach wherein the questions, although predetermined to a certain extent, could be adjusted flexibly to elicit more in-depth responses depending on the question. This method allows the interviewer to accommodate the respondent's worldview easily and discuss new ideas on this theme<sup>9)</sup>.

### *Questions*

In semi-structured interviews, we asked participants these questions.

Examples

- What did you think about your illness when you were diagnosed?
- What did you think about your treatment before you know this clinical study?
- How did you know about this clinical study?
- When you know this clinical study, how did you think about it?
- Why did you decide to receive an explanation of this clinical study?

- What did you think after the explanation?
- What did you think before you decided to participate?
- What did you think until the clinical study?
- What did you think among the clinical study?
- After the clinical study, what did you think?

### *Qualitative Analysis*

Analyses utilized the modified grounded theory approach (hereafter, M-GTA), a qualitative research method suited for qualitative data analysis. The M-GTA has excellent explanatory power for human behaviors related to social interaction and demonstrates analytical strength within a limited range, and is thus considered effective in the field of human services<sup>10)</sup>. Furthermore, as a rough standard, it can summarize results using data from as few as 10 cases<sup>10)</sup>. Our analysis targeted patients with DCM who participated in a clinical study, and focused on "psychological processes experienced there in by patients with DCM." From the qualitative data, we extracted contents worth noting in sentence form, and each of these was treated as an "example" to which a "concept definition" was appended based on its inferred meaning, along with a title generated as a "concept." Moreover, any other content that appeared to correspond to the generated concepts was extracted from the qualitative data and included in the originally extracted examples. In each case, consistency between the example and its definition as well as concept was

examined. Furthermore, the opposite meaning of the generated concept was considered and incorporated in this process, so as to prevent the viewpoint from being skewed. As a result, concepts that did not match multiple corresponding examples from participants were disregarded as unfounded, or new concepts were generated that embodied other examples. These analyses were conducted repeatedly for all data until no further generation of concepts was possible. These analyses generated concepts for which a minimum level of validity was guaranteed. Furthermore, a diagram of results illustrating the concepts and categorical relationships between concepts was created, along with a storyline explaining the diagram.

#### *Ethical Considerations*

This study was approved by the Kitasato Institute Hospital Research Ethics Committee.

## **Results**

### *Participants*

Among participants of a clinical study on immunoabsorption therapy for DCM, 12 who visited our hospital for follow-up examination from April 2011 through May 2012 were provided with an explanation regarding the present study, and 11 provided written consent to participate (9 men, 2 women; mean age  $\pm$  SD = 52.7  $\pm$  9.2 years).

### *Analysis*

Participant narratives were recorded and direct transcript of the recording, which

were used as qualitative data in the subsequent analysis. Mean interview duration was 38.4  $\pm$  34.6 minutes (range, 15-76 minutes).

A total of 19 concepts were generated and grouped into categories (Table 1). The results are summarized in diagram (Figure 1) and described in the storyline below.

### *Explanations of generated concepts*

[Sense of lack in medical technology]

Patients felt that the medical care they desired was not available to them. In the case of one patient, it can be inferred that the patient did not even acknowledge the previous treatment as a therapeutic intervention. The patients felt limited by the medical technology available at the time, which developed in them a feeling similar to resignation. It is possible that patients participate in clinical studies because their desired treatment is not available through regular medical care. This could be deduced from another patient, who stated "I would have not participated had I been able to receive treatment to my satisfaction."

[Dissatisfaction with the medical care environment]

Patients were dissatisfied with the medical care environment around them, which not only included medical staff but also encompassed the entire medical care system. One patient's narrative suggests that they had negative feelings toward staff members who did not provide the desired treatment. Moreover, some patients showed that they were dissatisfied with the current state of medical care as a whole. It is likely

Table 1 Concepts that comprise the psychological processes experienced by patients with dilated cardiomyopathy who participated in a clinical study

First category	Second category	Third category	Concept	Concept definition
PATIENT WHO DIDN'T KNOW THE CLINICAL STUDY	Feeling trapped	Sense of lack in medical technology		From the early phase of treatment, patients (as one of many patients) compared themselves with other patients.
			Dissatisfaction with the medical care environment	Patients sensed the limitations of current medical technology and exhibited feelings similar to resignation.
		Accidental discovery	Patients felt that it was by sheer luck that they became aware of the new therapy and its clinical study.	
PATIENT WHO DISCOVERED THE CLINICAL STUDY	Appreciation for the clinical study	Hopefulness	Hope for the desired environment	Patients anticipated a different environment with the new therapy, which included staff members who perform the treatment that is more akin to what they desired.
			Expectation for therapeutic value	Upon learning about the new therapy, patients came to anticipate positive results that might be brought about in terms of their own disease treatment.
		Concern for the unknowns	Patients were concerned about the fact that this is a clinical study, as well as aspects such as the content of the treatment which they had never experienced before.	
	Psychological escape	Decision to participate	Desire to escape from the current situation	Patients earnestly hoped for a change from the current situation in which they felt trapped and unable to receive their desired treatment.
			Recognition of the clinical study as the only way to escape	Patients regarded the clinical study as the only way that might allow for escape from the current situation.
			Prediction of overwhelming hopelessness	When making the decision regarding participation, patients experienced anxiety as they predicted a desperate situation where, if participation was not possible, they would be back in their original situation.
PATIENT WHO PARTICIPATED IN THE CLINICAL STUDY	Hope arising from confirming participation		Relief brought by confirming participation	Once participation was confirmed, participants felt relieved to be released from the anxiety of going back to the desperate situation.
			Joy of successful escape from hopelessness	Participants rejoiced in being able to escape from the helpless situation.
	Experience desired for themselves		Moving to desirable environment	Patients felt that they received treatment of their choice from the staff and institution they found to be desirable.
			Desirable therapeutic experience	Patients felt they received treatment of their choice.
	Feeling of fulfillment		Satisfaction of "being treated"	After completing the clinical study, patients were satisfied with the fact that they were given a "treatment," which was not possible when they were feeling trapped.
			Fulfillment found in therapeutic effects	Patients realized the therapeutic effects and felt satisfied.
PATIENT WHO COMPLETED THE CLINICAL STUDY	Setting a desirable future		Future of medical care environment	Patients pondered future medical care systems and the desirable state of medical care.
			Patient's own future	Patients considered their goals and hopes for their future life and treatment.
			Compassion for those who did not participate in the study	Patients felt indebted to those who did not participate in the clinical study, and were thinking of the feelings and the benefits for those patients.

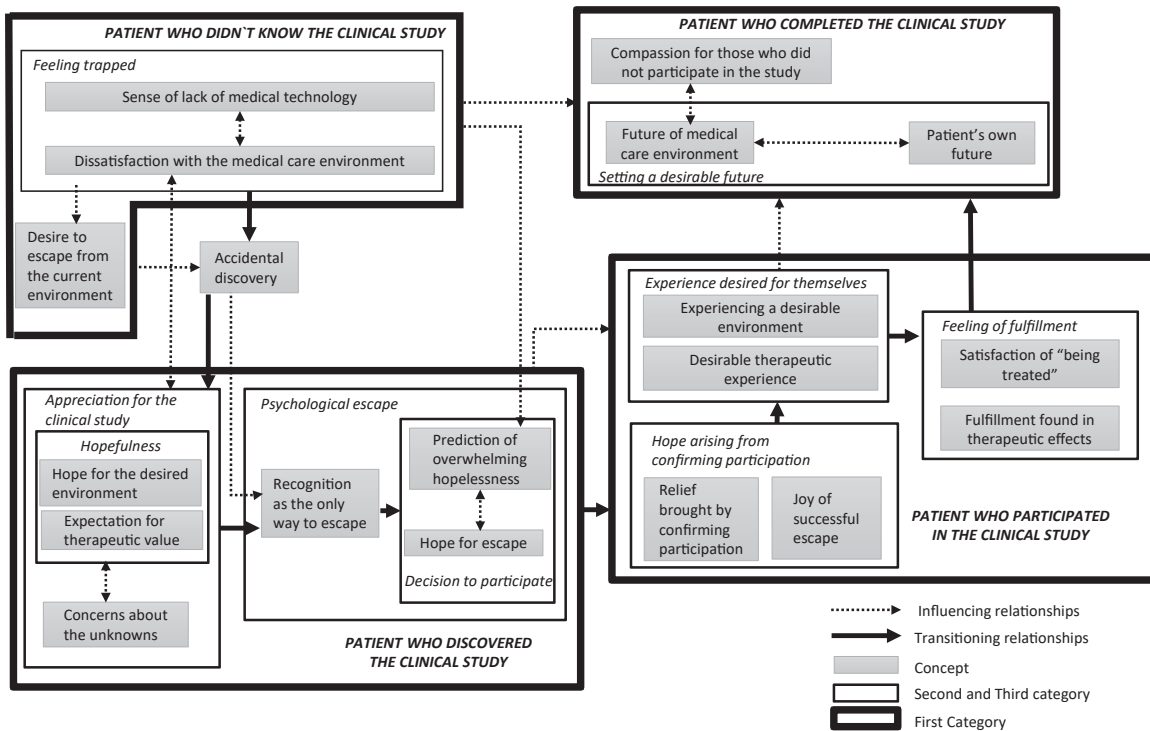


Figure 1 Psychological processes experienced by patients with dilated cardiomyopathy who participated in a clinical study

that negative images are not only created due to “dissatisfaction with the medical environment,” such as medical staff and medical care systems, but are also related to thoughts about medical technology itself (i.e., “sense of lack in medical technology”).

[Accidental discovery]

Patients felt that it was by sheer luck that they found out about the new therapy or its clinical study. Although the majority of patients learned about the clinical study through sources other than the medical staffs involved in their treatment, some patients obtained the information directly from the investigator of the study. In either case, patients were conscious of the accidental nature, acknowledging that it is well beyond their ability to even know about therapies being studied.

[Hope for the desired environment]

Patients anticipated a different environment (compared to previous ones), including staff members who would administer treatments more in line with what they had hoped to receive. In this context, the undesirable environment is the one experienced prior to knowing about the clinical study. While the impact of therapeutic effects was indeed significant, patients mentioned that they felt expectations for the different environment prior to study participation, suggesting that they were conscious about the new environment regardless of therapeutic effects.

[Expectation for therapeutic value]

Upon learning about the experimental

therapy, patients came to anticipate positive results that might be brought about in terms of their own disease treatment. Patients had extremely high expectations. Some patients even found hope in the fact that they had more options, in addition to the content of the clinical study itself. According to one patient, such feelings emerged while being fully aware of the possibility that the therapy might not necessarily prove effective.

[Concern for the unknowns]

Patients were concerned because the study involved a treatment that lacked official approval, and because the treatment content and components were such that they had not yet experienced. They were aware of the uncertainties of treatment effects and medical practice involved in the clinical study, and found these to be somewhat worrisome.

[Desire to escape from the current situation]

Rather than hoping for therapeutic effects, patients hoped for a change from the current situation, in which they felt helpless and trapped.

[Recognition of the clinical study as the only way to escape]

Patients regarded the clinical study as the only way that might enable them to escape from their current situation. In reality, patients may actually have other new ways to proceed with their treatment may outside of the clinical study, but patients viewed their discovery of the therapy (closer to their desired treatment) as

“sheer luck,” and thus perceived it as the only treatment available to them.

[Prediction of overwhelming hopelessness]  
When making decisions about participation in the clinical study, patients were anxious, feeling that their inability to participate would indicate a return to their original environment. This is largely related to the fact that clinical study participation is perceived as the “only” way by which patients might escape from their actual situation.

[Hope for escape]  
Patients were hopeful about the prospect of escaping from their current situation where they were unable to do anything about their disease. While they realized that efficacy was not guaranteed, they had more hope for the new therapy (which was closer to what they desired) relative to that for the current therapy, and decided to participate.

[Relief brought by confirming participation]  
Patients felt relieved when their participation was confirmed, as they felt released from the anxiety of returning their desperate situations. They were relieved to not be stuck in a state characterized by a “feeling of overwhelming hopelessness.” This feeling was predicted in the series of events, and patients reported a sense of being saved.

[Joy of successful escape from hopelessness]  
Patients rejoiced when they escaped from

their helpless situation, and exhibited a growing hope. It is likely that in cases where the decision to participate was not spontaneous, patients may not have found this same hope.

[Moving to a desirable environment]  
Patients felt they were able to receive treatment from medical staff at the institution of their choice. The unique clinical study environment with the presence of a clinical research coordinator (CRC), also seemed to be influential.

[Desirable therapeutic experience]  
Patients felt that they were able to receive the treatment they chose for themselves, through their participation in the clinical study.

[Satisfaction of “being treated”]  
After completing the clinical study, patients were satisfied with the fact that they were given a “treatment,” which was not possible when they were in a state where they felt trapped. In addition to the effects the study had on their disease, patients found value in the experience of participating in a clinical study, which is an experience the majority of society will never have.

[Fulfillment found in therapeutic effects]  
Patients realized the therapeutic effects and felt fulfilled. All patients who were interviewed in the present study felt some effects. However, these therapeutic effects did not necessarily correspond closely with numerical values. For example, some patients didn’t feel enough therapeutic effects.

[Future of medical care environment]

Patients pondered the optimal state of medical care based on their own experience with the clinical study, noting several aspects of the medical care environment that they hoped would be changed. One patient was conscious of benefits to other patients, while another patient was conscious of his/her own treatment. Both of these cases were included in this concept of patient consciousness about the medical care environment as a whole, given that it is likely not possible to clearly separate between oneself and others.

[Patient's own future]

Patients had goals and hopes for their future life and treatment. One patient was thinking about his goals in terms of his work. In other cases, the medical procedure itself was set as the goal, while others considered undergoing this treatment once again as a specific hope.

[Compassion for those who did not participate in the study]

Patients felt indebted to those who did not participate in the study, and were well aware of their feelings as well as the possible benefits of the clinical study for other patients. They perceived differences between themselves and other patients, as they were the ones who received the treatment.

### *Storyline*

Patients who participated in a clinical study for DCM, an intractable disease, faced their disease thinking that they were similar to other patients with DCM who suffered

from the same condition in the early stages after diagnosis, and shared the feeling that they were one of many patients with DCM.

In general, patients had become somewhat resigned to accept the current state of medical technology, which offered no effective treatment. They were frustrated about this environment, which included a system that did not allow them to receive the treatments they desired and medical staff that could not perform such treatments. Under those circumstances, they believed that they were not being treated, and that to continue on this path would only lead to a decline in their condition, ending in a feeling that they had lost and were trapped. As such, they desired to escape from the current environment, with the hope of ending up in a better situation.

In that context, the accidental discovery of a new therapy and its clinical study brought them hope as a new option. They were also hopeful and had positive feelings about the medical staff who could perform the treatment they desired. At the same time, however, they still worried about the unknown, or other aspects of medical care that they had not yet experienced. Still, they appreciated the chance to participate in a clinical study that allowed them to receive a test treatment for their intractable disease, versus their current state of continuous decline and feeling of being trapped.

This appreciation was combined with their original desire to escape. They viewed the clinical study as the only means of escape, and felt fortunate to have



discovered it. They decided to participate in the clinical study, thinking that it was the only way to change their current situation. At that point, amidst the hope for escape, they felt a great deal of apprehension, imagining the despair of falling again into a helpless situation if they were to lose this only option. Psychologically, they were not in the state of helplessness that made them feel trapped, but rather in a condition where they managed to mentally escape from the impasse, and some direction toward the means, i.e., the clinical study, could be seen.

The anxiety they felt at the time of decision-making disappeared when their participation was confirmed. At this time, they felt joy at being released from the previous state of deadlock, in which they harbored many unsatisfied feelings. Feeling of hope arose from the confirmation of their participation in the clinical study.

After that, they received the treatment they chose for themselves in the context of the clinical study, and through interactions with medical staff involved in the process, they believed that they were able to assess what is desirable in the state of medical care.

After completing the clinical study, patients felt satisfaction in knowing that their desired “treatment” was performed in the end, felt fulfilled with the therapeutic intervention as well as the very fact that they were able to place themselves in such an environment. They had a sense of well-being.

When considering the major categories, patient perception changed over the course of the study; after receiving a diagnosis,

patients perceived themselves as one of many patients who had the same disease. They then perceived themselves as those who were able to discover the clinical study by chance, and after participating and going through the study without any incident, they perceived themselves as those who participated in a clinical study.

On that basis, patients were conscious, not only of themselves, but other patients with the same disease and their desired image of future medical environments as well.

## Discussion

In this study, we conducted an interview survey targeting patients who participated in an investigator-initiated clinical study on immunoabsorption therapy for DCM. Participants had DCM, a disease with a poor prognosis, usually treated with standard therapy mainly consisting of symptomatic treatment for heart failure and prevention of further disease progression<sup>1)</sup>. While previous studies have shown that process of decision-making concerning participation in a clinical study<sup>6, 8)</sup> as well as experience participating in a clinical study<sup>7, 11)</sup> have various effects on participants' psychology, the present study was novel to theorize psychological processes in DCM patients from the time before participation in the clinical study through its completion.

Participation in a clinical study may have become a means to receive “treatment” for patients with intractable diseases, for whom standard therapy is not effective or for whom there are no prospects of achieving full recovery with

standard therapy<sup>12</sup>). Surveys targeting patients with cancer who participated in a phase I clinical study have shown that some patients had “expectations for investigative treatment”<sup>13, 14</sup> or hoped “to get better”<sup>14</sup>, which served as decision-making factors regarding clinical study participation. Moreover, some patients who participated in a clinical study on heart disease had an “expectation of better treatment”<sup>15</sup>. We predicted that the participants of the present study would also have similar expectations from the clinical study regarding therapeutic effects<sup>16-19</sup>. Participants analyzed in this study had enormous anxiety (predicted as a sense of overwhelming hopelessness) from the time of decision-making regarding participation in the clinical study until official confirmation of their participation. Patients with DCM experience a lower QOL compared to the general population and are often more anxious and depressive<sup>20</sup>. Thus, these patients are more prone to suffer from both physical and psychological pain. In addition to their daily physical and psychological burden, patients who anticipate an escape from the pain of disease by undergoing an experimental treatment (clinical study) are placed in uncertain situations, such as not knowing about their participation, which only increases the anxiety. Such levels of uncertainty may also exist among patients who could not participate in the clinical study, but as these patients were not included in the present survey, we couldn't extrapolate on their thoughts. The damaging effects on patients who were unable to participate in the clinical study

(i.e., those for whom this anxiety was realized) should be taken into consideration when recruiting clinical study subjects.

As shown in the Figure1, the transition from being “patient who didn't know the clinical study” to “patient who discovered the clinical study” was triggered by an “accidental discovery,” and our participants perceived this transition to be very challenging. They also recognized the clinical study that they found through sheer luck as “the only way.” This suggests that patients have tremendous anxiety, i.e., “a sense of overwhelming hopelessness” about having to return to their original state. Currently, information regarding therapies and clinical studies can be obtained on the Internet, if patients actively seek to collect it. However, this is still somewhat insufficient under present circumstances in Japan<sup>21</sup>. In fact, patients are aware of the difficulty of discovering clinical studies, and thus there is room for improving methods of accessing clinical study information. It may be necessary for medical staff to be more proactive about providing information to patients on new therapies and clinical studies. Japanese Ministries have initiated a “5 yearly clinical study activation plan 2012” from 2012, “Ethical guidelines on medical research for human subjects” from 2014 and “Clinical Trial Act” from 2018, and they are trying to promote clinical study publically and encourage participation from the general public<sup>22-24</sup>.

Several limitations of the present study should be noted. The present study only included interviews performed at the time of clinical study completion, and thus

patients had positive images concerning the study content. As such, interviews with patients who had negative views regarding the study, or those who could not participate in the clinical study, were not included in the collected data. This may have biased the results. Moreover, only limited number of participants were recruited for this study because the number of clinical research volunteers were limited. Future studies should take the present study results into account and allow for the inclusion of such patients.

### **Conclusion**

Our study showed that patients have high expectations regarding clinical study participation, not only for the treatment it offers but also with respect to medical staff involved in the study who perform the desired treatment. Moreover, we found that patients are highly aware of the medical environment that surrounds them, including systems pertaining to medical care as well as medical staff. This awareness is cultivated by their experiences from the time before they learned about the clinical study through completion of the study. In particular, they were keenly aware of the difference between the previous environment in which they received no satisfactory therapies and the environment they placed themselves in through the experience of a clinical study. Hence, in regard to treatment after the clinical study, they hoped to be in an environment where they would be able to interact with their desired medical staff, even if they could not receive the new therapy.

The findings of this study reveal an importance in the capacity for medical staffs to interact with patients at the level of general medical care by taking into account the patient's attitude, even if they are unable to provide patients with a new therapy on the spot. Furthermore, it will also be necessary to consider the burden on staff who respond to the expectations of these patients. This study may be informative the importance to understand the psychological statement of the intractable disease patients.

### **List of abbreviations**

DCM; Dilated cardiomyopathy

NYHA; the New York Heart Association

CRC; clinical research coordinator

### **Declarations**

#### **Ethics approval and consent to participate, consent to publish**

This study was approved by the Kitasato Institute Hospital Research Ethics Committee.

Participants were given an explanation regarding the present study, and provided written consent to participate in this study. Our data doesn't report on individual patient data.

#### **Availability of data and materials**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

#### **Competing interests**

There is no conflict of interests in this study.

## Funding

No funding was received.

## Authors' contributions

YI and NT designed the study protocol, monitored data collection for the whole trial, analyzed the data, and drafted and revised the paper. EA initiated the collaborative project, designed the study protocol, monitored data collection, analyzed the data, and drafted and revised the paper. AB designed the study protocol, monitored data collection for the whole trial, and revised the draft paper.

## Authors' information

EA is an associate professor and a Ph.D. in Clinical Pharmacy. YI has Bachelor of Pharmacy degree (a six-year course) and is a pharmacist. NT is a Ph.D. in Medicine. AB (MD, Ph.D.) is a cardiovascular specialist.

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## References

1. Hunt SA, American College of C, American Heart Association Task Force on Practice G. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). *J Am Coll Cardiol.* 2005;46 (6):e 1 -82. doi:10.1016/j.jacc.2005.08.022.
2. Baba A, Akaishi M, Shimada M, Monkawa T, Wakabayashi Y, Takahashi M et al. Complete elimination of cardiodepressant IgG3 autoantibodies by immunoabsorption in patients with severe heart failure. *Circ J.* 2010 ; 74 (7) : 1372-8.
3. Dandel M, Wallukat G, Englert A, Hetzer R. Immunoabsorption therapy for dilated cardiomyopathy and pulmonary arterial hypertension. *Atheroscler Suppl.* 2013 ; 14 (1) : 203-11. doi:10.1016/j.atherosclerosis.2012.10.029.
4. Gho JM, Kummeling GJ, Koudstaal S, Jansen Of Lorkeers SJ, Doevendans PA, Asselbergs FW et al. Cell therapy, a novel remedy for dilated cardiomyopathy? A systematic review. *J Card Fail.* 2013 ; 19 (7) : 494-502. doi: 10.1016/j.cardfail.2013.05.006.
5. Developmental Promotion Committee of Japan Human Sciences Foundation. Perspective for medical-care needs in 2020. In: Japan Health Sciences Foundation. Tokyo. 2011. pp. 144
6. Kohara I, Inoue T. Searching for a way to live to the end: decision-making process in patients considering participation in cancer phase I clinical studies. *Oncol Nurs Forum.* 2010 ; 37 (2):E124-32. doi:10.1188/10.ONF.E124-E132.
7. Kelly C, Ghazi F, Caldwell K. Psychological distress of cancer and clinical study participation: a review of the literature. *Eur J Cancer Care (Engl).* 2002 ; 11 (1) : 6-15.
8. Broun R, Albrecht TL. Enrolment in clinical studies. In: Kissane D, Bultz B, Butow P, Finlay I, editors. *Handbook of Communication in Oncology and Palliative Care.* UK: Oxford University Press; 2010. pp. 231-43.
9. Sharan B M. *Qualitative Research and Case Study Applications in Education: Revised and Expanded from Case Study Research in Education.* San Francisco: Jossey-Bass ; 1998.
10. Uwe Flick, Ernst von Kardorff and Ines Steinke. *A Companion to Qualitative Research.* UK: SAGE Publications;2004. pp. 253-258

11. Gargiulo M, Herson A, Michon CC, Hogrel JY, Doppler V, Laloui K et al. Attitudes and expectations of patients with neuromuscular diseases about their participation in a clinical study. *Rev Neurol (Paris)* . 2013 ; 169 (8-9) : 670-6. doi:10.1016/j.neurol. 2013.04.005.
12. Haruka Nakata, Sachie Yoshida, Etsuko Arita, Kaori Muto, The Timing of Decision-Making and Informed Consent: Patients's Perspective and Experiences of Clinical Trials in Japan, *Jpn J Clin Pharmacol Ther* 2017 ; 48 (2) : 31-19
13. Agrawal M, Grady C, Fairclough DL, Meropol NJ, Maynard K, Emanuel EJ. Patients' decision-making process regarding participation in phase I oncology research. *J Clin Oncol*. 2006 ; 24 (27) : 4479-84. doi: 10.1200/JCO. 2006.06.0269.
14. Kass N, Taylor H, Fogarty L, Sugarman J, Goodman SN, Goodwin-Landher A et al. Purpose and benefits of early phase cancer trials: What do oncologists say? What do patients hear? *J Empir Res Hum Res Ethics*. 2008 ; 3 (3) : 57-68. doi:10.1525/jer. 2008.3.3.57.
15. Yuval R, Halon DA, Lewis BS. Patients' point of view in heart failure trials. *JAMA*. 2001 ; 285 (7) : 883-4.
16. Sam Horng and Christine Grady. Misunderstanding in Clinical Research: Distinguishing Therapeutic Misconception, Therapeutic Misestimation, & Therapeutic Optimism *IRB: Ethics & Human Research* Vol. 25, No. 1 (Jan. - Feb., 2003), 11-16
17. A.M. Stiggelbout, A.H.Pieterse, J. C.J.M.DeHaesb, Shared decision making: Concepts, evidence, and practice, *Patient Education and Counseling* Volume 98, Issue 10, October 2015, Pages 1172-1179 Author links open overlay panel
18. Cathy Charles, Amiram Gafni, Tim Whelan, Shared decision-making in the medical encounter: What does it mean? (or it takes at least two to tango) *Social Science & Medicine* Volume 44, Issue 5, March 1997, Pages 681-692
19. Cathy Charles, Amiram Gafni, Tim Whelan, Decision-making in the physician-patient encounter: Revisiting the shared treatment decision-making model *Social Science & Medicine* Volume 49, Issue 5, September 1999, Pages 651-661
20. Steptoe A, Mohabir A, Mahon NG, McKenna WJ. Health related quality of life and psychological wellbeing in patients with dilated cardiomyopathy. *Heart*. 2000 ; 83 (6) : 645-50.
21. Arita E. Review of useful contents of clinical studies on a website and development of clinical studies portalsite for the general public. 2013. <http://mhlw-grants.niph.go.jp/index.html>. Accessed 30 Oct 2015.
22. Ministry of Health, Labour and Welfare, and Ministry of Education, Culture, Sports, Science and Technology (Japan). 5 yearly clinical study activation plan 2012 [Japanese]. 2012. [http://www.mhlw.go.jp/topics/bukyoku/isei/chiken/dl/121025\\_3.pdf](http://www.mhlw.go.jp/topics/bukyoku/isei/chiken/dl/121025_3.pdf). Accessed 13 Jun 2019.
23. Ministry of Health, Labour and Welfare, and Ministry of Education, Culture, Sports, Science and Technology (Japan). Ethical guidelines on medical research for human subjects [Japanese]. 2014. <https://www.mhlw.go.jp/file/06-Seisakujouhou-10600000-Daijinkanboukouseikagakuka/0000153339.pdf>. Accessed 19 Jun 2019.
24. Ministry of Health, Labour and Welfare, Clinical Trial Act [Japanese], 2018. <https://www.mhlw.go.jp/file/06-Seisakujouhou-10800000-Iseikyoku/0000213334.pdf>. Accessed 19 Jun 2019.