

第13章

臨床試験の情報提供とコミュニケーション

なぜ臨床試験において情報提供が大切なのか。CRCの役割を研究マネジメント、データマネジメント、患者支援に分けてその理由を考えてみたい。

研究マネジメントは、試験遂行に関係する部門間(病棟・外来・検査部など)や医師、コメディカルとの業務調整やスケジュール管理が挙げられる。スケジュール管理には、個々の患者に関する管理と、試験全体の管理がある。患者ごとのスケジュール管理は、来院や入院の日程の調整、薬物動態など、各種検査の採血時間や食事・試験薬内服のタイミングを説明し、理解してもらうことなどである。

一方、試験全体のスケジュール管理は、試験開始までに必要な準備を整え、あらかじめ、予定された期間内に症例登録が達成できるよう試験全体の進捗管理をすることである。

これらのマネジメントのためにもコミュニケーションスキルは重要である。

データマネジメントは、適切な時期に必要なデータを得て、速やかに提出するための調整となる。そのためには、来院日を守るなど、患者の協力も必要となる。

患者支援には、自己決定の支援と、そのための情報提供や、試験や治療に対する不安等の対応がある。患者からの信頼を得られてこそ必要なデータを得ることにつながる。

情報提供とコミュニケーションには密接な関係がある。

いうまでもないことであるが、CRCとして患者に信頼されるためには、対応なども含めたコミュニケーションスキルが不可欠である。

CRCは、多くの場合、初対面の患者に臨床試験について説明を行い、同意の意思確認を行う。その際には、患者が試験参加について意思決定するための十分でわかりやすい情報提供が必要であり、その過程で患者との間に信頼関係が生まれる。信頼関係が生まれるとさらによりコミュニケーションがとれるようになるのである。

一方で、当然のことではあるが、医師と患者の間には、情報の量や内容の不均衡が存在し、コミュニケーションの障害になることがしばしばある。CRCには、そ

の不均衡を調整する役割が期待される。

1. CRCによる情報提供の重要性

CRCが臨床試験に関する情報提供を行うことは、試験参加に関して患者の自己決定支援のために重要であるが、試験に参加している患者の安全確保と試験の正確性を担保するためにも重要となる。

a. 患者に情報提供の大切さを理解してもらう

患者の安全確保のためには、患者から適切な時期に正しく情報提供してもらうこと、副作用の対処法を理解してもらうことが必要である。臨床試験では適格基準を満たした患者を登録しなければならない。検査データなど測定できる基準はよいが、既往症・合併症・自覚症状などは本人からの情報提供が元になる。本人が使用している薬をすべて教えてもらわなければ、併用禁止薬を服用しているかどうか確認ができない。漢方薬・健康食品・サプリメントなどには相互作用のある場合もあり、情報把握が必要である。

こうした情報を正しく提供してもらわないと不適格な患者を登録してしまう可能性がある。また、思わぬ有害事象が発現するなど患者に不利益となる恐れもある。

試験開始後は、自覚症状の発現時期や程度を正しく伝えてもらうことは、データ収集上、必要であるばかりではなく、早期に適切な処置を行うことにつながる。さらに試験中に行う検査の意味や採血条件(空腹時・内服前か後か、など)も患者に十分理解してもらっておかなければ適切なデータを得るための協力が得られない。

情報提供は試験の正確性を担保するとともに患者の安全を守ることになりCRCは患者と信頼関係を築くことが求められる。

b. 有害事象が発現した際の対応と報告の重要性を知ってもらう

試験に参加した場合、試験中に起こりうる有害事象について、いつ頃起こるか、どのようなことが起こるか、起こったらどうすればよいかをあらかじめ情報提供しておけば、患者自身が慌てることなく対処できる。こうした有害事象に関する情報は、患者が最も知りたいことの1つであり、説明文書も重要な情報提供のツールとなる。

抗悪性腫瘍薬の臨床試験では、必ずといっていいほど有害事象が発現するため、つらくて途中で試験参加をやめたいときも、そのことを伝えることができる関係でなければならない。

しかし、臨床試験への参加を、患者からやめるとはいいだしにくいこともある。一方で試験治療を続けたいために、自覚症状について患者が報告しないこともあるかもしれない。CRCには言葉によるコミュニケーションだけでなく、態度や表情などから読みとれる能力も必要である。

2. コミュニケーションの6つのポイント

患者とのコミュニケーションには大きく分けて6つのポイントがある。

a. オープニング

初対面の時には、まず、あいさつと自己紹介を行う。CRCが何をする人かを説明してもよい。同席者については、できれば患者との関係を確認するとよい。

また、いきなり試験の説明に入らずに、相手がリラックスして説明を聞くことができるよう環境を整えることも大切である。

b. 共感的態度

良好なコミュニケーションをとるためには、話しやすいように目線や態度などにも注意が必要である。大げさすぎない笑顔で対応するなど表情にも気を配るとよい。

相手と目線の高さを合わせるように、立ったままではなく座って話をするにより、落ち着いて話をすることができ、重要な情報を収集できることも少なくない。

会話中には、適度に相手の目を見る、うなづく・相槌を打つ・会話を促すことも大切である。それにより、相手が自分の話を聞いてもらっていると感じることができる。また、事実を確認する言葉として「…と医師にいわれたのですね」など相手の言葉を繰り返す、「つらかったんですね」などの言葉をかけるとよい。

患者の話は、できる限り、妨げずに聞くほうがよいが、訴えが長い場合や横道にそれている場合は、話をまとめるなどして時間内に必要な情報を得るようにする能力も必要である。

c. 傾聴

がん臨床試験に参加する患者は自分自身の病気以外にもさまざまな不安を抱えていることが多い。

患者のさまざまな思い(病気に対する考え・家族への思い)や不安(治療に対する考え、生活設計、仕事などを含めた経済的問題)に耳を傾けることはよりよいコミュニケーションにつながり、重要な情報を得られることもある。患者の家族の会話も同様である。患者本人が、有害事象について過小に報告することもあるので身近にいる家族からの情報収集が有効な場合もある。

ただし、診察や検査の予約時間や自分自身の業務を考慮すること、適切な部署を紹介するなど自分の立場を考えた節度ある対応が必要である。

d. 説明・対応の方法

説明や対応は、時と場所を選ぶことが大切である。

患者自身に説明を聞く余裕がない場合もあり、CRCの状況にもよるが、その場で十分に時間がとれないときは、患者にその旨を伝え、相談したうえで、日時を改めて設定することが望まれる。

説明場所は、可能であれば診察室から少し離れた個室などが望ましい。

相手を尊重するという意味で原則として丁寧な言葉遣いを心がけるほうがよい。

説明に際して、専門用語はわかりやすく言い換えるなどが必要であるが、患者によっては治療歴が長いなどの理由で言い換える必要がないこともある。病歴や背景についてはカルテなどからわかる範囲で調べてもよい。

試験の内容についてはCRCが自分の言葉で説明できるよう、不明確な点は事前に医師などに確認しておきたい。なお、病状に関する説明などは、医師に直接説明してもらうように促す、あるいは診察に同席して、説明を依頼できるように配慮を行う。

e. 患者教育

患者が試験内容について理解できていない部分を確認、補足説明し、不安なところを補うことが求められる。そのうえで選択肢を示し、自己決定ができるようサポートを行う。

試験の内容など大まかなこと(スケジュール、点滴か内服か、入院か外来通院の

みか)は必ず理解してもらう必要がある。試験治療も、外来通院で行うことが多くなっているため、日常生活上の注意や有害事象が発現時の対処法など自己管理できるように情報提供が必要となる。

外来診察時は時間に限りがあるので、必要なことは要領よく医師に伝えることができるよう、CRCが診察前に情報を整理するとよい。

f. クロージング

最後に話忘れたことはないか、他に聞きたいことはないか、一言確認するとよい。また、次回の来院予定なども確認しておくとうい。

CRCにとってコミュニケーションスキルは十分な情報を得るためにも、提供するためにもとても重要である。

特にがんという疾患の特殊性から、患者やその家族の心情にも配慮し、表情や話しかたなどにも十分に気をつけて対応することが望まれる。

がん臨床試験に参加する患者にとって、CRCは医師や看護師より身近でコミュニケーションをとりやすい心強い存在であることが多い。また、そうした存在でなければならない。

けれども、CRCがすべて一人で対応するのではなく、必要に応じて、該当する部署のスタッフに対応を依頼、引き継ぎを行うとうい。

3. がん臨床試験におけるインフォームドコンセント

インフォームドコンセントとは、治療や検査などの医療行為について、患者本人が十分な説明を受け、理解し、納得したうえで同意することである。インフォームドコンセントに基づいて医療を受けることは、患者の自己決定権、すなわち基本的人権の1つとして保証されているものであり、臨床試験に限らず日常診療においても大切なことである。これは医療行為が少なからず侵襲を伴うからであるが、それに加えて臨床試験では、「治療効果や安全性について不確実性(uncertainty)が高く、リスクが大きい」などの理由により、日常診療の場合以上に詳細な説明が必要とされ、患者自身による自発的同意が臨床試験へ参加する際の必須条件となる。

本項では、がん臨床試験のインフォームドコンセントにおける留意事項について述べる。

[Original Article]

A Survey on Biostatistical Consulting at Japanese Medical Institutes

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ABSTRACT

This article reports a survey on biostatistical consulting at Japanese medical institutes, which included the information on when, where and to whom statistical consulting is provided. The results of our survey bring to light the various empirically-predicted problems involved in biostatistical consulting in Japan, where the demand of biostatisticians has grown rapidly. We discuss the issues making comparisons among the results of this survey, and the surveys in the United States and Germany. (Jpn Pharmacol Ther 2014 suppl 1 ; 42 : s33-s44)

KEY WORDS Statistical consulting, Biostatistics, Survey

1. Introduction

The importance of statistical consulting in academic institutes has been discussed since pragmatism is fitted to be the philosophic foundation in modern science¹⁾ and widely accepted not only for improving the quality of the research but also for its financial utility²⁾ or educational application.^{3~5)} It has been vigorously discussed on how to organize the statistical consulting unit in colleges,⁶⁾ universities,^{7~9)} and clinical research institutes^{10,11)} especially in the

United States. The most of study conclusion reached is that a separately funded consulting center operated as a division of a department of statistics is the most appropriate way to provide statistical consulting, then, there exist more than 80 statistical centers or units in the United States or other research universities at the time when this paper is written in 2013 (http://www.cstat.msu.edu/beyond/other_centers_other_univ.aspx).

However, few of the articles on statistical consulting report empirical data regarding what statisti-

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日本における医学統計コンサルテーションに関する実態調査

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Table 1 Backgrounds of the biostatistical consultation units which have the open website for consultation

	Number of units	%
Country		
USA	19	70.3
Canada	3	11.1
Other	5	18.5
Institutional type		
University	14	51.9
Medical institute	7	25.9
School of Public Health	3	11.1
College	3	11.1

cal consultants actually do. One of those is an earlier work by Niland et al.¹²⁾ investigated the organizational structures, salary ranges, sources of funding, computer resources and operational concerns of biostatistical consulting units in the North America. They pointed out the issues in providing biostatistical consulting in research institutes at that time, such as inadequate institutional funding, lack of coauthorship on collaborative manuscripts or insufficiency of time for independent research as major issues. The more recent work by Gullion and Berman¹³⁾ got an overview of the activities of statistical consultants in any fields, i. e. business, education, agriculture, ecology, medicine, public health, manufacturing, engineering, and so on. It showed that consultants in clinical research had the highest percentage of PhDs and had the fewest years of experience and the statistical practice pattern is also much different from those of statisticians in other fields. Another recent work by Windman and Kauermann¹⁴⁾ gave a view into the practice of statistical consulting at German universities and showed that the culture of consulting is better developed in medicine than in business and economics, which is much difference in the United States. Their observations suggest it is important to consider cultural background, educational system in statistics and other backgrounds and current situations in each country when we discuss how to organize biostatistical consulting.

In order to get information on the operational structures, procedures, infrastructure and common concerns for the activities of biostatistical consulting in Japan, we conducted a survey of Japanese academic clinical research centers or hospitals taking the statistician's point of view. This paper presents a summary of the survey discussing the issues making

an international comparison.

2. Methods

2.1 Population and Procedure

We found there were 15 academic clinical research centers or hospitals in Japan, in which a department, section or unit of biostatistics were founded at least three years ago with at least one statistician at a junior faculty level. This restriction was imposed because it was considered we needed at least three years to accumulate a certain amount of experience of statistical consulting at each center. We use hereinafter the word "unit" to refer to a department, section or unit of biostatistics in each clinical research centers or hospitals.

For each of the clinical research center or hospital defined above a contact person was approached by e-mail and invited to fill out an online questionnaire.

2.2 Questionnaire

The questionnaire consists of 20 questions to get an overview of who (Q8 and Q13), to whom (Q3 and Q4), and how (Q10 and Q11) statistical consulting is provided. Q1 and Q2 ask demographic information of clinical centers/hospitals. We asked which items from a list of 27 choices were often requested as the contents of a consultation (Q5). To make the list of choices for this question, we did a survey for 27 open websites of consulting units in the United States and other countries which clearly stated the subjects which area are offered for biostatistical consultation, because there was no previous report for this subject to our knowledge, while there was a report for more detail topics for biostatistical consultation in Deutsch et al.⁴⁾ Among 27 websites, 70% websites were managed by the statistical units in the United States, and 51% units were affiliated with the university (Table 1). Based on the result shown in Table 2, we chose the topics included in Q5. Respondents could specify in a text field in Q6 a response that we did not provide in Q5.

We also asked how much time is spent for statistical consulting (Q9 and Q12), fee for consultation (Q14 and Q15), general results of the first consultation (Q7) and whether statistical consulting is incorporated in the teaching program of the biostatistical section (Q16). Additionally there were open questions to answer concerns in providing biostatistical consulting at the affiliated center/hospital and items

Table 2 Subject area/topics for biostatistical consultation appeared on the websites of biostatistical consulting units in other countries

area/topics for consultation	number of units	%
data analysis/statistical analysis of data	22	81.5
designing study/study design	20	74.1
sample size/power analysis	20	74.1
results interpretation	11	40.7
database management/cleaning	10	37.0
grant application/proposal	9	33.3
report/publication writing/manuscript preparation	9	33.3
data presentation/data visualization	9	33.3
guidance on statistical software	7	25.9
data monitoring	7	25.9
protocol review	6	22.2
response to manuscript/publication reviewer	6	22.2
questionnaire design	5	18.5
protocol development	5	18.5
collection of data	4	14.8
data interpretation	4	14.8
survey design	4	14.8
interpretation of statistical methods	3	11.1
application of statistical methods	3	11.1
sampling design	3	11.1
development of specialized statistical methods	3	11.1
multivariate modeling	3	11.1
model fitting	3	11.1
randomization schemes	3	11.1
database creation	3	11.1
survey analysis/data	3	11.1
Bioinformatics	2	7.4
IRB submission/resubmission	2	7.4
paper reviews	2	7.4
trial design	1	3.7
study conduct	1	3.7
Survival analysis	1	3.7
mixed modeling	1	3.7
hypothesis testing	1	3.7
Inferential statistical analysis	1	3.7

which the responder would try to improve in the future. The questionnaire in Japanese can be viewed online (<https://sites.google.com/site/biostatnccgmjp/project-4>), and its English version is provided as an appendix to this paper.

3. Results and Discussion

Among 15 biostatistical units in each research center or hospital, 14 units responded to the survey (response rate : 93.3%). Out of these 14 statistical units 8 units are affiliated with the national or public university, 3 units are affiliated with the private university, and 3 of them are the national advanced

medical research centers. All 14 units provide biostatistical consultation, and half of them affiliated with national or private university offer consulting both internally and externally, and the other half of them offer only internal consultation.

3.1 Who provide statistical consultations to Whom?

The total number of staff for biostatistical consultation is 1-3 in 12 out of 14 statistical units. Only other 2 units (14.3%) affiliated with the private or public university have a middle size unit (4-10 staffs). There is no larger size unit with more than 10 staff which is observed in the North American or European countries. For reference, in 1995 in the

Table 3 Type of staff member for biostatistical consulting in each clinical center/hospital

Type of staff member		Number of units with employee (s) in category	(%)
National advanced medical centers (<i>n</i> =3)	Professor level (Director)	1	1/3 (33)
	Associate professor level (Chief)	1	1/3 (33)
	Assistant professor/Post doctorate level (Research scientists)	2	2/3 (66)
Universities (<i>n</i> =11)	Professor level	5	5/11 (45)
	Associate professor level	7	7/11 (64)
	Assistant professor level	8	8/11 (73)
	Student	1	1/11 (9)
	Medical Doctor	2	2/11 (18)

Table 4 Number of consulting cases per month by unit size

Unit size	Number of consulting cases per a month			
	2-3	4-7	8-15	>15
1	1	0	2	1
2-3	1	3	4	0
4-10	1	0	0	1
(<i>n</i> =14)	3 (21%)	3 (21%)	6 (43%)	2 (14%)

United States, it is reported that 17 out of 31 (54.8%) biostatistical units employed more than 10 staff members.¹²⁾ In German paper in 2007,¹⁴⁾ 63% or consulting units in medical institutes were categorized into 'large unit', which was defined as those who employed more than one chair or single chair with a number of lecturers/senior lectures. **Table 3** shows the type of staff member in biostatistical consulting units. 79% units are organized with at least one senior (associate professor/professor) level statistician. Compared to the results of the survey in the North America in 1995,¹²⁾ it is distinct that the Masters/Bachelors level biostatisticians are not much employed in each section/unit and there are still clinical centers in which medical doctors are conducting statistical consultation. Additionally only one unit provide an opportunity for students to take part in biostatistical consulting activity although most of centers are affiliated with the university.

We also asked to whom statistical consultation is offered. Among 7 units which offer not only internal but also external consultation, 5 (71%) units offered only for researchers and students affiliated with academic institutes and another 2 units offered not only for people affiliated with academic institutes

but also for people affiliated with industry for free. Details about the results and discussion of fee for consultation is described in section 3.4.

3.2 How statistical consulting provided?

All units offered face-to-face oral consulting and 12 (86%) units offered e-mail consulting. Furthermore, 7 (50%) units offered telephone consulting. Only 1 unit offered online consulting, for which would be expected to increase demand with the developments in information technology.

We asked the time spent on a consultancy case by a multiple choice question with the outcomes 15 min, 30 min, 1 hour, 2 hours and not-determined. 64% of the cases needed more than 1 hour, which observation is almost the same as the results of the survey in German medical schools.¹⁴⁾ Another 36% of the units responded that the time for consultation was not determined.

We also question the number of requests received in a categorical scale with outcomes every day, a few times per a week, once in a week, a few times per month, once in a month, once in a half year and once in a year. **Table 4** shows the number of consulting cases are not associated with the unit size and the marginal distribution of number of consulting cases per month was almost the same as the numbers shown in German survey. Hence, it is suggested that statistical consulting would not be organized properly appropriate for the number of researchers in each institute and the total amount of grant that are awarded during a year. Furthermore, taking the results described in Section 3.1 together, the average number of cases per consultant per month in Japan would be relatively large compared to those

Table 5 Area or subjects for biostatistical consultation

area/subjects for consultation	number of units	(%)
Study Planning Phase		
Study planning/Study design/Protocol development	13	92.9
Sample size/Power analysis	13	92.9
IRB submission/resubmission	9	64.3
Protocol review	9	64.3
Statistical Analysis Plan/Documentation for statistical analysis	8	57.1
Grant application/proposal	7	50.0
Reporting Phase		
Data analysis	13	92.9
Report/publication writing/manuscript preparation	12	85.7
Response to manuscript/publication reviewer	12	85.7
Others		
Paper reviews	8	57.1
Data management	6	42.9
Programming	6	42.9
Simulation	4	28.6
Grant reviews	4	28.6
Data presentation/Data visualization	2	14.3

in Germany and the North America.

3.3 Area and subject of statistical consulting

As we mentioned in Section 2, a list of subjects for statistical consultation was made based on the result in **Table 2** and personal communication with some Japanese statisticians. **Table 5** shows that the major subjects of statistical consultation in Japan are apparently the same as those in other countries. According to the additional question, however, 100% units offered not only statistical “consultation” but also statistical practice within the framework of statistical consultation. In German, 89% of statistical consulting units in Medical science offered only oral consulting and only other 11% offered oral consulting including statistical analysis.¹⁴⁾ Hence biostatistical consulting in Japan implies pursuing or helping with the analysis of data and it is suggested that contents of statistical consultation in Japan would be different from those in other countries even in the same area or topics.

3.4 Fee for consultation

We did not ask much about financial aspects of a statistical consulting but just asked if the sections/units charged for internal or external consulting service. 57% units offered only free consulting service, and the other 43% units charged for external or internal consultation, however, all of them answered that the

consulting fee depends on the situation, which implies they seem not to have a fee schedule for their consulting service, or it does not work even if it exists. It could be therefore no unit answered specifying fee for consulting in the unit.

3.5 Consultation leads to collaborative studies?

We also question whether consultation leads to collaborative studies and a chance to get co-authorship because the discussion in Niland’s paper¹²⁾ and our experience show that it is statisticians’ big concern. 4 (29%) units answered that statistical consultation lead little chance to get collaborative project and another 10 (71%) units answered statistical consultation lead only collaborative studies without payment (5 units) or granted collaborative studies in which statisticians could participate in one of investigator (5 units). We should note that we did not ask if statistical co-authorship was received routinely. It is described in Niland’s paper that “the investigator is sometimes less likely to extend co-authorship when biostatisticians bill for their time and effort.” Additionally, “it was suggested that only time spent in more routine tasks such as data entry and programming be charged back to investigators, and more conceptual activities such as proposal design, grant, and manuscript preparation be provided without charge to maintain a collegial relationship with investigators.” It would be suspected that many present Japanese

biostatisticians would be suffering from a similar situation back in 90s in the United States. According to the International Committee of Medical Journal Editors (<http://www.icmje.org>) : "All persons designated as authors should qualify for authorship, and all those who qualify should be listed. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content. Authorship credit should be based only on :

- ①a) substantial contributions to conception and design or
 - b) acquisition of data or
 - c) analysis and interpretation of the data
 - ②a) drafting of the article or
 - b) revising it critically for important intellectual detail
 - ③a) final approval of the version to be published.
- Conditions 1, 2, and 3 must all be met."

Based on the guideline like above mentioned, now some American institutes issue a guideline for determining co-authorship for biostatisticians. It is suggested that biostatistician need to know what is the authorship and to be trained how to collaborate with investigators to be an author of a scientific paper as well as investigators are need to be educated how to collaborate with biostatisticians.

3.6 Consulting is used as practical training?

Described in Section 1, it has been well debated that statistical consultation is effective for understanding of statistics and practical skills in statistics. In German,¹⁴⁾ 21% of the units in Medical science departments included internal consulting cases in the curriculum. However, in our survey, there was no institute which used statistical consulting as practical training for junior biostatisticians. As described in Section 3.1, there was only one unit in which a student joined as a consultant, suggesting that there would be few institutes which utilize statistical consulting for education. However, the corresponding questionnaire item does not ask clearly about the educational use of statistical consulting for students cooperated with the university, so it would be future work to assess educational use of statistical consultation in more detail.

3.7 Concerns of statisticians

Finally we question whether the statisticians have

some concerns about biostatistical consultation. The answers from 7 units are summarized as follows.

- 1) Almost works for consultation are doing without any instructions or regulations.
- 2) Staffing problem (especially for shortage of manpower)
- 3) Funding issues

Regarding the issue 1), this problem which could be originated in Japanese fuzziness culture would be a big problem especially in academic institutes not only for work for consultation but also for any work in clinical research. Someone is doing something somehow to someone makes sometimes a critical mistake. Additionally, time and effort are not usually explicitly regulated and allocated for biostatisticians by the universities or research institutes. Currently some institutes in other countries issue guidelines for estimating biostatistician effort. For example, it is clearly mentioned in the guidelines of University of California Davis School of Medicine¹⁵⁾ that "We strongly recommend that biostatisticians be actively involved throughout the grant proposal development process," and "In general, funding for faculty and staff should not fall below 10% of total effort per statistician per time period on a single project. Although there occasionally are valid reasons for a lower level of effort on particular projects, intervals with funded effort falling below 10% require approval by the division chief for faculty and by the CTSC* biostatistics director for CTSC staff." Furthermore, effort is allocated by the size of projects and the level of statisticians in the guidelines. Prompt attention to this issue should be made in each institute, and it is desirable to develop a guidelines for biostatistician effort or/and a working instruction for biostatistical consultation based on experience in the initiative institutes with sufficient experience in biostatistical consulting.

It has been well debated for concerns in the issue 2) and 3) in Niland et al.¹²⁾ and other papers.^{1,6,7,9)} From those discussions, consultation units especially in the United States have been changing their approach and structures. At present in Japan, staffing concern was almost limited to shortage of manpower, however, like as in the United States, it could be substantially developed for shortage of appropriate level of statisticians along with the increase of demand for consultation for advanced statistical problems with popularization and improve-

*CTSC : Clinical and Translational Science Center

ments of curriculums in Biostatistics in medical schools in near future.

As concerns in funding, careful considerations would be needed to compare discussions especially in the United States with our concerns because budget size for research and its funding structure in Japan is so different from those in the United States, although which has been dynamically changing due to economic crises.^{16,17)} Concerns in funding have inextricable link between the deep-rooted problems in research funding structure in Japan, such as unequally-distributed research funding at the institution and individual levels.¹⁸⁾ One of the reason why statistical consulting units are not funded or do not charge for consultation would be that many clinical research themselves are not well funded.¹⁹⁾ It should be a great difficulty to have a fundamental change in such funding structure in Japan, while each unit could clarify the utility of statistical consultation to some extent to make clear the contents and the time consumed for consultation.

4. Conclusion, study limitation and future research implications

Our survey provided a first view of biostatistical consulting activity in Japanese medical institutes, from which information is likely to be of interest both to biostatisticians (consultees) and medical or clinical researchers (consulters). It is suggested that the subjects for statistical consultation are similar but its contents and work environments for consultants in Japan would be much different from those in other countries, especially from those in the United States. Additionally, the current concerns about biostatistical consultation in Japan are almost the same as those in the United States discussed 20 year ago (e. g. in Niland et al.¹²⁾). The culture of consulting seems to be weakly developed for biostatistical sections in Japan, while the biostatisticians is likely to feel overloaded with the work not so much consultant as data analyst.

There are some limitations of this study. First, our survey could not be complete census of the population we assumed. It is possible that we did not get information for some biostatistical units in medical research institutes because we could not get the list of all biostatistical units in Japan which was publicly available such as a list of America Statistical Association on the website, however, the biostatistical units in Japanese representative medical research institute

were included in our survey. Additionally, our survey population does not include biostatisticians who are working in the medical university or other educational departments, such as department of public health, pharmacology or engineering. It would be expected that the results of our survey could be devastating if such populations were included, because, to our knowledge, most of departments in Japanese university do not have any system and evaluation standards for statistical consultation. It is very hard to recognize and survey such latent biostatisticians. To study on such population, we would expect that our research would activate serious discussion about statistical consulting among Japanese statistical associations or other formal organizations.

As we mentioned in the result section, we did not ask much about the topic of funding issues because we considered Japanese were very sensitive to the question about money issues. Our survey showed that more than half of units offered only free consulting service. However, the topic of consulting fees, including factors making up budgets and methods of billing, often comes up in discussion among statistical consultants,¹³⁾ and it is important to clarify especially for the unit without any consulting fee about how the unit is organized and how much it costs to keep biostatistical consultation for a certain medical research institute. Further investigation would be needed for this topic.

According to the report released from Ministry of Health, Labour and Welfare in 2006,²⁰⁾ only 9 out of 346 institutes or hospitals employed biostatistician, and the average number of biostatistician per institute was reported as about only 1 for the university hospital ($n=4$). Compared to the content of the discussion in the report with our results, we might say that the number of institute with biostatisticians is increased and the demand for biostatisticians has been rapidly increasing compared to 8 years ago, however, the number of biostatisticians per one institute is not increased. Additionally, our survey suggested that the concern of biostatisticians is not so changed and working environment for biostatisticians in medical institutes would not be so improved during the last 7 years. Biostatistical consulting activities in Japanese medical institutes or research hospitals have only just begun. We believe our results will be of some help to develop and promote statistical consulting activities in Japanese medical institutes.

Acknowledgement

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Appendix :

A questionnaire survey about biostatistical consultation service (in English)

Let's answer!

This questionnaire survey is being taken in order to better understand the actual state of biostatistical consultation services in the Japanese academia, and also to serve as materials for discussions on what types of services shall be provided in the future. The result of the survey is scheduled to be reported to statistics-related societies and journals, while keeping the information on individual institutions confidential upon obtaining your agreement.

We would be grateful if you could answer all the questions in this questionnaire, and greatly appreciate for your understanding and cooperation.

Q1

Which one of the following categories applies to the institution that the respondent is affiliated with?

- National or Public university
- Private university
- National advanced medical research center
- etc.

Q2

Please specify your primary affiliation.

Q3

Biostatistical consultation services being :

- Provided externally as well as internally by the institution.
- Provided only internally, as public services of the institution.
- Provided only internally, by tacit understanding.
- Not provided at present, but I would like to see it provided in the future.
- Not provided at present, nor do I want to see it provided in the future.

If you answered "Provided" to Q3, please answer Q4. If you answered "Not provided" to Q3, please skip Q4-Q17 and continue from Q18.

Q4

Biostatistical consultation is being provided to (Please check all that apply) :

- Doctors and/or researchers affiliated with the institution
- Doctors and/or researchers affiliated with the mother institution
- Students affiliated with the institution
- Students affiliated with the mother institution
- Associates of doctors and/or researchers affiliated with the institution
- Associates of doctors and/or researchers affiliated with the mother institution
- Associates of students affiliated with the institution
- Associates of students affiliated with the mother institution
- Doctors and/or researchers not affiliated with the institution
- Students not affiliated with the institution
- Biostatisticians not affiliated with the institution
- Corporate doctors and/or researchers
- Corporate Biostatisticians

NOTE :

- 1) "The mother institution," means, for example, in case of a university, the entire university, including academic departments, laboratories, centers, and any other institutions affiliated with the university.
- 2) "Associates" refer to collaborators and companions.

Q5

Please choose the type of consultation being provided. (Please check all that apply)

- Consultation related to research planning
- Consultation related to grant application
- Actual work related to grant application
- Consultation related to study protocol application
- Actual work related to study protocol application
- Consultation related to sample size estimation
- Actual work related to sample size estimation
- Consultation related to statistical simulation studies
- Actual work related to statistical simulation studies
- Consultation related to working instructions for data management
- Actual work related to working instructions for data management
- Consultation related to statistical analysis plans
- Actual work related to statistical analysis plans
- Consultation related to preparation of working instructions for statistical analysis
- Actual work related to preparation of working instructions for statistical analysis
- Consultation related to analytical programming
- Actual work related to analytical programming
- Consultation related to statistical analysis (other than programming)
- Actual work related to statistical analysis (other than programming)
- Support for manuscript writing
- Consultation for data visualization
- Support for data visualization
- Support for, and actual work on, making replies to the reviewers
- Grant review
- Protocol review
- Review for manuscripts
- Others

Q6

If you selected "Others" in Q5, please state specifically as to what other work is being conducted.

--

Q7

What is the usual development after the first consultation session is provided?

- Consultation ends after the first session.
- Consultation ends after the second session.
- Consultation continues through the third session or longer.
- It turns into a volunteering-like joint research project.
- It turns into a revenue-generating joint research project such as role-divided research.

Q8

Please select who is providing the consultation.

- Professor level Biostatisticians
- Associate Professors level Biostatisticians
- Assistant Professor level Biostatisticians
- Master or under level biostatisticians
- Students in the department of biostatistics
- Other students
- Medical doctors
- Statisticians
- Others

Q9

Please select an applicable category related to the time length of a consultation session.

- 15 minutes
- 30 minutes
- 1 hour
- 2 hour
- 3 hours or longer
- No set time length

Q10

Please select the consultation method being used. (Please check all that apply)

- Face-to-face
- Telephone
- Web (Internet)
- e-mail
- Others

Q11

If you selected "Others" in Q10, please state specifically as to what other consultation methods are being used.

Q12

Please select the frequency of consultation being provided.

- Almost every day
- Twice to three times a week
- Approx. once a week
- Approx. twice to three times a month
- Approx. once a month
- Approx. once every six months
- Approx. once a year

Q13

Please select the number of staffs that are providing consultation in your section.

- One
- Two persons
- Three persons
- More than three persons but less than 10 persons
- More than 10 persons

Q14

Please select the fee structure of consultation.

- Free consultation in all cases.
- Free consultation for any client for the first session, paid consultation from the second session.
- Free consultation for any client for the first session, paid consultation from the second session for external clients (internal clients need not pay).
- Internal clients need not pay in all cases. External clients must pay from the first session.
- All clients must pay from the first session.
- Depends on the case.

Q15

If you selected "Depends on the case." in Q14, please state specifically as to what kind of fee setting is being used.

Q16

Is consultation-related training being offered to statisticians?

- Yes
- No

Q17

If there is any issue related to consultation services being provided by your institution, please let us know.

Q18

If there are any biostatistical consultation services you would like to enhance, please list them.

Q19

This question is only intended for the respondents that stated that there are no biostatistical consultation services being provided. Please state specifically as to why that may be the case.

Q20

Please select from the following concerning the publication of the aggregated result of this questionnaire survey.

- I consent to publication through presentation at academic societies and publication in a scientific journal.
- I only consent to publication through presentation at academic societies.
- I only consent to publication in a scientific journal.
- I do not consent to publication of any sort.

Please submit!

Q17 臨床試験・治験とは？



「人」を対象として何らかの実験的介入(治療・診断・看護ケア・予防等)を加えてそのアウトカム(結果)を評価する「介入研究」のうち、介入の単位が個人であるものを「臨床試験」と言う(介入の単位が地域や職場である場合は「地域介入研究 / 職場介入研究」と呼ぶ)。

臨床試験のうち、厚生労働省から医薬品や医療機器の製造販売承認を得ることを目的として行うものを「治験」と呼ぶ(「臨床治験」と言う人がいるが何を指すか明確でなく使うべきではない)。

治験には企業主導治験と(2003年の薬事法改正により可能となった)医師主導治験があり、企業主導の治験や製造販売後臨床試験以外の医療者 / 研究者による臨床試験を「研究者主導臨床試験」と呼ぶ。後者は長いので単に「臨床研究」と呼ばれることがあるが、本来の「臨床研究」は「介入研究」と「観察研究」を含む広い概念(治験を含む概念)なので治験の対義語として使うのは正しくない。短く呼ぶなら英語の「investigator-initiated trial」の略の「IIT (アイアイティー)」がよいと思われる。

治療についての臨床試験は「治療開発」を目的として行われるが、治療開発は「相 (phase)」と呼ばれる段階を踏んで漸進的に行うべきという考えが国際的なコンセンサスである。一般に医薬品開発の「相」が、以下の第Ⅰ相～第Ⅳ相とされているが、考え方は医療機器、手術手技、放射線治療、集学的治療の開発も同じである。

第Ⅰ相：人に安全に投与 / 実施できるかどうかを探索する段階

第Ⅱ相：当該疾患(対象集団)に対する有効性があるかどうかを探索する段階

第Ⅲ相：標準治療よりも良い治療であるかどうかを通常はランダム化比較試験にて検証する段階

第Ⅳ相：市販後の日常診療で広く使われて初めてわかるような、長期投与による毒性(時に有効性も)や稀な毒性を調べる段階

本来、治療開発の「相」と各相で行われる試験の「種類 (type)」は別の概念だが、「がん」の治療開発においては第Ⅰ相で臨床薬理試験を行って推奨用量を決定し、第Ⅱ相でがん種を特定して有効性を探索し、第Ⅲ相でランダム化比較試験による検証を行うことが定形化されているので、試験名として「第Ⅰ相試験」、「第Ⅱ相試験」、「第Ⅲ相試験」と呼ぶことが一般的になっている(他の疾患領域では必ずしもそうではないことに注意が必要)。

臨床試験においてアウトカムを測る「ものさし」を「エンドポイント (endpoint)」と呼び、各

試験で試験の結論を下すのに一義的に用いられるエンドポイントを主たるエンドポイント (primary endpoint) と呼ぶ。

第Ⅰ相試験では用量制限毒性 (dose limiting toxicity : DLT), 第Ⅱ相試験では奏効割合, 第Ⅲ相試験では全生存期間 (overall survival : OS), 無再発生存期間 (relapse-free survival : RFS), 無増悪生存期間 (progression-free survival : PFS) 等が primary endpoint とされることが一般的だが, 手術の第Ⅱ相試験で治癒切除割合を用いたり, 奏効割合がエンドポイントとして適切でない分子標的薬の第Ⅱ相試験でランダム化第Ⅱ相試験としてPFSを用いたり, 試験の対象や治療の特性によって適切なエンドポイントが選択される。

(福田 治彦)

特集

免疫療法の逆襲を現実化した免疫checkpointの修飾

免疫療法の臨床評価に
関する問題点*

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Key Words : immune-checkpoint inhibitors, FDA guidance, Fleming-Harrington test, immune-related Response Criteria

はじめに

2011年に抗CTLA-4抗体であるipilimumabが米国で承認され, 2014年7月に抗PD-1抗体であるnivolumabが日本で承認されるなど, 免疫チェックポイント阻害薬が現実的に実臨床に導入される時代がやってきた。今後もさらに多くの免疫治療薬の開発が進むことが期待されるが, 迅速に臨床現場に導入されるためには臨床試験による正しい評価が欠かせない。一方で, 免疫療法はその作用機序から, 治療後の一時的な腫瘍増大や, その後の腫瘍縮小など独特の効き方が観察されることが知られており, その点を考慮に入れた臨床評価法が提唱されている。

本稿ではがんワクチンの評価について書かれたFood and Drug Administration (FDA) ガイダンスの枠組みを用いてphaseごとの免疫療法の臨床試験デザインの考え方を紹介するとともに, 近年免疫療法の領域で見かけるようになったFleming-Harrington検定, そしてimmune-related Response Criteria (irRC) の考え方と問題点について

述べたい。

がんワクチンについての
FDAガイダンス

2009年にFDAの生物製剤部門であるCenter for Biologics Evaluation and Research (CBER)は, 製薬企業向けのがんワクチン評価のガイダンス“Guidance for Industry- Clinical Considerations for Therapeutic Cancer Vaccines”の「案」を公表し, その後2011年に正式に公表した¹⁾。がんワクチンが抗腫瘍効果を発揮するための一連の免疫応答には一定の時間を要するため, 効果の発現までがこれまでの抗がん剤より遅くなるという特徴があり, そのために臨床試験のデザインにも従来の抗がん剤とは異なる考え方が必要になるということが, このガイダンスが出された背景にある。免疫チェックポイント阻害薬のようなリンパ球の表面分子群をターゲットとするような薬剤は, がんワクチンとは異なる作用機序を有することからこのFDAガイダンスの対象外とされているが, 免疫チェックポイント阻害薬でも同様に抗腫瘍効果の発現が遅れて現れる現象が知られており²⁾, デザイン自体の考え方には参考となる記述が多い。以下にガイダンスで述べられている各phaseのデザイン上の留意点を,

* Methodological issues in clinical trials of cancer immunotherapy.

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