Japan Clinical Oncology Group

Policy No. 38
Title：Intergroup Study
Applicable Range: All members in the JCOG (researchers, members of various committees, and staff of the JCOG Data Center/Operations Office).

Intergroup study

1. Basic Principles

JCOG has been engaged in research on biomarkers with progress made on identification of biomarkers for many types of cancer. Compared to the past, clinical trials now tend to target a more specific subject population.

An important mission for JCOG is to establish the standard treatment for rare cancers which are not usually targeted by the pharmaceutical industries for their drug development.

Based on these backgrounds, the chances of the collaboration with study groups outside of JCOG as well as intergroup study within JCOG are increasing also in the view of accelerating patient accrual.

Collaborative studies may involve the intergroup study by the multiple internal study groups in JCOG working together and the intergroup study by collaboration with external study groups (Cooperative groups).

This policy focuses on both types of the intergroup studies mentioned above and stipulates the scope of JCOG intergroup studies and how they are managed.

2.Terminology

Terms used in this policy are defined as follows:

1） **Intergroup study**: defined as clinical research conducted by two or more groups.
2） **Intergroup trial:** Intergroup studies that are interventional studies (clinical trials)
3） **Central support organization functions:** Activities of the central support organization of a study group that support protocol development/review, data management, central monitoring, adverse event reporting/review, and site visit audit etc.
4） **JCOG Internal Intergroup Study:** A JCOG study jointly conducted by two or more JCOG study groups
5） **JCOG-led Intergroup Study:** A study conducted jointly with external study groups where JCOG acts as the leading group that formulates the clinical trial plan, and performs the main activities, including data analysis.
6） **JCOG Participating Intergroup Study:** An intergroup study in which an external study group other than JCOG performs the primary analysis.

3. Intergroup study

How an intergroup study is executed is shown below according to the type and timing.

3.1. Procedure for Intergroup Studies by Type of Study

3.1.1. JCOG Internal Intergroup Study

Clinical research conducted jointly by two or more study groups within JCOG. JCOG Data Center/Operations Office is responsible for central support organization functions.

3.1.2. JCOG-Led Intergroup Study

As the leading group, JCOG formulates a trial plan, and the JCOG Data Center/Operations Office are responsible for main central support organization functions, including data analysis.

There are three following ways to implement the trial:

1） Single protocol using a single data center

A single protocol is used, and patient registration, database management, and adverse event reporting are all performed by the JCOG Data Center/Operations Office.

At the time of this policy formation, the JCOG Data Center/Operations Office do not support this type of intergroup trial. Anyone wishing to conduct this type of trial must consult with the JCOG Data Center/Operations Office.

2） Single protocol using multiple data centers

A single protocol is used, and patient registration, database management, and adverse event reporting are performed by each group (Cooperative group); however, interim, primary, and final analyses are performed by the JCOG Data Center.

At the time of this policy formation, a several domestic intergroup trials by JCOG and WJOG are being conducted as this type.

3） Multiple protocols using multiple data centers

Each group has each independent study protocol and conducts its own patient registration, database management, and adverse event reporting.

The JCOG Data Center conducts data analyses, such as interim, primary, and final analyses. This type of study is called “parallel study” in which the framework of the trial, including eligibility criteria, protocol treatment, examination schedule, and method of statistical analysis, are consistent among the groups. However, other details may vary among the groups to allow for flexibility.

A hypothetical case would be where patient registration and data management are carried out independently by each group, but, data from all groups are integrated at the JCOG Data Center at the time of data analysis.

In the case of (2) and (3), where the primary analysis or final analysis method/procedure for each study is specified in each individual protocol, a plan should be made in advance for integration of data from all groups for the primary analysis or final analysis, which is conducted after completion of patient registration, and described in each individual protocol.

3.1.3. JCOG Participating Intergroup Study

A study group external to JCOG formulates the study plans and the applicable group conducts main central support organization functions, including data analysis.

The JCOG Data Center/Operations Office may or may not conduct central support organization functions.

There are following three ways to implement the trial:

1) **Single protocol using a single data center.**

A single protocol is used. Patient registration, database management, and adverse event reporting are all performed by a central support organization of a study group outside JCOG.

Participating JCOG sites perform patient registration and adverse event reporting according to the method prescribed in the intergroup study protocol.

In the example of an intergroup study with EORTC, patient registration, data submission, and adverse event reporting are performed directly into the EORTC Data Center by active sites in Japan. The JCOG Data Center/Operations Office engages in coordination of activities between active sites in Japan and the EORTC Data Center but is not involved in data management or statistical analysis.

2) **Single protocol using multiple data centers**

A single protocol is used. Patient registration, database management, and adverse event reporting are performed by each group (Cooperative group); however, interim, primary, and final analyses are performed by the central support organization of a study group outside JCOG. Although there is no precedent at the time of policy formation, this would be applicable to an intergroup trial between JCOG and WJOG that was led by WJOG.

3) **Multiple protocols using multiple data centers**

Each group has an independent study protocol and executes its own patient registration, database management, and adverse event reporting.

Central support organizations of study groups outside JCOG conduct data analyses such as interim, primary, and final analyses.

A hypothetical case would be where, in what is known as a “parallel study”, integration analysis is performed at a data center outside JCOG.

Although there is no precedent at the time of policy formation, this would apply if the Japan–Korea intergroup study JCOG0705/KGCA01 (REGATTA study) conducted by the Stomach Cancer Study Group (SCSG) was led by the Korean group.

In the case of (2) and (3), where the primary analysis or final analysis method/procedure for each study is specified by each group’s individual protocol, a plan should be made in advance to integrate the data from all groups for primary analysis or final analysis, which is conducted after completing patient registration and described in each individual protocol.

3.2. Procedure for Intergroup Studies according to Participation Stage

Intergroup studies may be divided into two types depending on the participation stage: 1) a study conducted as an intergroup study from the initial time of planning (newly planned), and 2) a study converted to an intergroup study after the start of the study (after protocol approval).

The review procedure for each scenario is as follows:

Table 1. Procedure for Intergroup Studies by Type and Participation Stage

Type of Intergroup Study (Applicable Committee)	Participation Stage Approval by the Administrator of the Medical Institution	JCOG Study Coordinator Involvement	Approval needed from the JCOG Executive Committee for Implementation of Intergroup Studies	Approval needed from Committees		
						(Applicable Committee)
JCOG Internal Intergroup Study	New Planning	Protocol Development	Yes*2	Yes PRC*3	Yes	Yes
	After the start of study	Protocol Revision	Yes	Yes DSMC*4	Yes	Yes
JCOG-led Intergroup Study/JCOG Participating Intergroup Study (Multiple DC)	Newly Planned	Protocol Development	Yes*2	Yes PRC*3	Yes	Yes
	After the start of study	Protocol Revision	Yes	Yes DSMC*4	Yes	Yes
JCOG Participating Intergroup Study (Single DC)	Newly Planned	(Protocol Development)	Yes	—	—	Yes
	After the start of study	(Protocol Revision)	Yes	—	—	Yes

*1 Approval is necessary from an administrator of the medical institution to which the Study Chair and the Study Coordinator are affiliated with.

*2 The review is conducted similarly to a review of a regular concept by the JCOG Executive Committee. If a study becomes an intergroup study at the protocol development stage after approval of the concept, approval by the Executive Committee is also necessary.

*3 PRC：JCOG Protocol Review Committee

*4 DSMC: JCOG Data and Safety Monitoring Committee

4.Planning of Intergroup Studies

4.1.1. Proposals at Group Meetings

When drawing up a new intergroup study or planning to convert to an intergroup study, the Study Chair/Study Coordinator or candidate for this role should make a proposal at a group meeting after receiving approval by the Study Group Chair.

4.1.2. Coordination with the JCOG Data Center/Operations Office

When the Study Group Chair decides to implement an intergroup study following agreement at the group meeting, the Study Coordinator will inform the Data Center/Operations Office immediately.

In the case of JCOG Internal Intergroup Study, the directors of the Data Center and Operations Office will be notified that approval from the Study Group Chairs of both study groups has been granted.

In case of JCOG Internal Intergroup Study, a "leading study group," which is responsible for protocol development and implementation of trials, should be determined.

In the case of a JCOG-led Intergroup Study or an intergroup study with JCOG participation using multiple data centers, regardless of whether the group is domestic or overseas, if JCOG has not previously participated in an intergroup study with the particular group, before discussion at the JCOG Executive Committee, the directors of the Data Center and Operations Office visit the central support organization of the group to evaluate their data management methods and other functions for determining whether an intergroup study is feasible.

If the directors of the Data Center and Operations Office consider that there are no problem and confirm the feasibility of the intergroup study, they should immediately notify those to the Study Group Chair, and the Study Chair.

In the case of JCOG Participating Intergroup Study using a single data center, the JCOG Study Coordinator candidate should inform the directors of the Data Center and Operations Office that approval from the chairs of both study groups has been granted.

Because the JCOG Data Center/Operations Office do not perform central support organization functions for such studies, the JCOG Study Coordinator candidate should contact the partner study group in a timely manner to check the status of protocol development and discuss the review procedure within JCOG with the directors of the Data Center and Operations Office.

Refer to "6. Participation Procedure for a JCOG Participating Intergroup Study (Single Data Center)" for additional details on the review procedure.

5.Procedure of Switching to JCOG Intergroup Study

5.1. Switching to JCOG Internal Intergroup Study

The procedure for switching to JCOG Internal Intergroup Study after concept approval, as well as addition of study group within JCOG, is as follows:

5.1.1. Discussion at Group Meetings

Each Study Chair/Study Coordinator involved in JCOG Internal Intergroup Study shall consult with the Study Group Chair and discuss about switching to an intergroup study at a group meeting.

5.1.2. Request for Review on Switching

If there is consensus within the study group about switching to JCOG Internal Intergroup Study at the group meeting, the Study Group Chair shall send a request of switching to JCOG Internal Intergroup Study to the JCOG Operations Office for review by the Executive Committee.

Documents to be submitted

- Request for review of an intergroup study: include the names of the group(s) involved and reasons for switching to an intergroup study. (Free format)
- Study Protocol
- Model Informed Consent Form

5.1.3. Review by the Executive Committee

A vote on switching to JCOG Internal Intergroup Study is conducted at a conference review by the Executive Committee following discussion among the JCOG Governing Committee. On the basis of the results of the review by the Executive Committee, the JCOG Chair issues a written notification on whether changing to JCOG Internal Intergroup Study has been approved.

5.1.4. Procedure after Review by the Executive Committee

The Study Coordinator should submit a revised protocol draft to the Data and Safety Monitoring Committee (DSMC) after approval by the JCOG Executive Committee for changing to JCOG Internal Intergroup Study.

Details of the review on protocol revision are as per JCOG Policy No. 21 "Data and Safety Monitoring Committee."

5.2. Changing to Intergroup Studies with Groups Outside JCOG (JCOG-led Intergroup Study and JCOG Participating Intergroup Study using multiple data centers)

This applies to scenarios where a group outside JCOG participates mid-course in a study conducted independently by a study group within JCOG or, alternatively, where JCOG participates mid-course in a study conducted by a study group outside JCOG.

5.2.1. Discussion at Group Meetings

The Study Coordinator or candidate should consult with the Study Group Chair at group meetings to discuss the pros and cons of changing to an intergroup study.

5.2.2. Request for Review on Switching to Intergroup Study

If group consensus is achieved for changing to an intergroup study at a group meeting, the Study Group Chair should make a request to the JCOG Operations Office for review by the Executive Committee.

Documents to be submitted

- Request form for a review of an intergroup study: include the names of the group(s) involved and reasons for changing to an intergroup study. (Free format)
- Study Protocol
- Model Informed Consent Form

5.2.3. Review by the Executive Committee

Whether switching to this type of intergroup study is approved or not is determined at a conference review by the Executive Committee after discussion by the JCOG Governing Committee.

On the basis of the results of the review by the Executive Committee, the JCOG Chair provides written notification on whether the change to an intergroup study has been approved.

5.2.4. Procedure after the Review by the Executive Committee

The Study Coordinator requests a review of the protocol revision of the JCOG study by the Data and Safety Monitoring Committee (DSMC) upon approval by the JCOG Executive Committee for switching to this type of intergroup study.

Details on the review of a protocol revision are as per JCOG Policy No. 21 "Data and Safety Monitoring Committee."

6.Participation Procedure for JCOG Participating Intergroup Study (Single Data Center)

Regardless of whether it occurs during trial planning or after trial activation, the procedures for participating in a JCOG Participating Intergroup Study using a single data center are as follows:

6.1. Participation in a JCOG Participation Intergroup Study (Single Data Center)

6.1.1. Request for Review on Participation

If group consensus is achieved for switching to an intergroup study at a group meeting, the Study Group Chair makes a request to the JCOG Operations Office for review by the Executive Committee

Documents to be submitted

- Request for review of an intergroup study: include the names of the group(s) involved and reasons for switching to an intergroup study. (Free format) The request should include the documents assuring that implementation system meets the conditions shown in 6.2.1.
- Study Protocol
- Model Informed Consent Form

6.2. Decision on Participation in a JCOG Participating Intergroup Study (Single Data Center)

6.2.1. Guidelines for becoming partner study group(s) in JCOG Participating Intergroup Study

When participating in a JCOG Participating Intergroup Study using a single data center, the leading group, which leads the intergroup study, should meet the following conditions regarding the study implementation system.

However, note that these are merely guidelines. Whether participation is approved is determined by the Executive Committee, along with consideration of other conditions.

- A permanent central support organization must exist and those personnel in leadership positions as well as the structure for accountability must be explicit.
- A dedicated data manager (DM) is required and a procedure for data management must be in place.
- The central support organization must have a system for monitoring, onsite auditing, and adverse event reporting.
- A biostatistician is involved in study planning, study conduct, and analysis (it does not have to be a full-time employee).

6.2.2. Process to Determine Participation

After discussion at a meeting of the JCOG Governing Committee, there is a vote on participating in a JCOG Participating Intergroup Study at a conference review by the Executive Committee

The review is conducted in accordance with JCOG Policy No. 04 “Ethical Principles.” The Executive Committee grants their approval only when the study has social/scientific value, scientific validity, fair subject selection, and favorable risk/benefit ratio and there is no problem.

If the Executive Committee determines that there is a problem, a status of "unapproved" or "conditional approval," which mandate that the issue is to be solved before approval, will be given.

"Approval" requires support from more than 2/3 of the members of the Executive Committee.

On the basis of the results of the review by the Executive Committee, the JCOG Chair provides a written notification on the decision regarding participation in an intergroup study.

A JCOG administration number, JCOGXXXX-INT, will be given to a JCOG Participating Intergroup Study (Single Data Center).

6.3. Report on the Implementation Status of Intergroup Studies (Single Data Center)

Regarding participating JCOG institutions to the JCOG Participating Intergroup Study using single data center, the Study Group Chair should monitor the situation at the participating institutions as well as patient registration status, and should submit the monitoring report and audit report annually to the Executive Committee.

7.Publication

When publishing the results of an intergroup study, a description of the research grant that supported the study should be included for both JCOG-led Intergroup Study and JCOG Participating Intergroup Study.

Refer to JCOG Policy No. 26 "Publication Policy" for details on the publication of results.