Planning and implementation of Japan-Indonesia joint study of skin cancer

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Abstrak

Masalah kanker kulit tampaknya merupakan masalah penting baik di Indonesia maupun di Jepang. Berdasarkan minat bersama telah dikembangkan penelitian kerjasama antara Indonesia dan Jepang. Telah dirancang penelitian meliputi tiga aspek, yaitu epidemiologi, klinik dan histopatologi. Kerjasama peneitian tersebut dimulai dengan pertemuan konsultatif dan pembinaan tim yang bersifat multidisiplin baik dari pihak Indonesia maupun Jepang. Dalam tahap persiapan dilakukan identifikasi masalah ilmiah, tujuan, makna dan keuntungan untuk kedua belah pihak, termasuk pertukaran pengetahuan, ketrampilan dan alih teknologi. Manajemen penelitian mengikuti lima fase, yaitu penetapan & perencanaan, perorganisasian, pengendalian dan penghentian, dengan penyesuaian untuk proyek penelitian dengan menerapkan lima unsur ilmu. Pengumpulan data direncanakan dengan penyusunan formulir baku untuk penelitian klinik, histopatologi dan kuesioner untuk penelitian epidemiologi, dilengkapi dengan pedoman untuk pewawancara. Pengorganisasian pengumpulan dan pemrosesan data melibatkan semua anggota tim menurut alur khusus dan jadual Gannt. Laporan kemajuan berkala dibuat setelah tiap pertemuan konsultatif. Baik persamaan maupun ketidaksamaan yang ditemukan di antarakasus kanker kulit Indonesia dan Jepang di analisa. Hasil-hasil preliminer dari penelitian kerjasama dipresentasikan dan dibahas dalam Simposium Sehari dan pertemuan ilmiah nasional dan internasional. Makalah-makalah akan dipublikasikan dalam suatu monograf di Medical Journal of Indonesia dan majalah internasional lain.

Abstract

Skin cancer appeared to be an important cancer problem in Indonesia and Japan. Based on common interest of the problem, a joint study between Japan and Indonesia on skin cancer has been established. Three fold-study, namely epidemiological, clinical and histopathological aspects have been designed. The collaborative study has been initiated by consultation meetings and building of multidiscplinary teams, for both Japanese and Indonesian sides. The preparation of the joint project has been initiated by the development of proposal with approval of the Dean and submitted to the Ministry of Education, Sport and Culture, Japan. The proposal includes the identification of scientific problems, the objectives, the significance and the merit for both sides, including exchange of knowledge, skill and transfer of technology. The management of the research project followed five phases, namely defining & planning, organization, controlling and termination, with adjustment to research project by applying five elements of science. The collection of data has been planned by developing standard forms for clinical study, histopathological study and questionnaire for epidemiological study, accompanied by its manual for interviewers. The organization of data collection and processing involved all team members following special flowchart and Gannt chart. Periodic progress report was made after every consultation meeting. Both similarity and dissimilarity of the findings between Indonesian and Japanese skin cancer cases were analyzed. Preliminary results of the joint study were presented and discussed in One Day Symposium and other national and international scientific meetings. The papers are to be published in a monograph in the Medical Journal of Indonesia and other international journals.

Keywords: *planning, implementation, joint study, skin cancer, Indonesia and Japan.*

The problem of skin cancer remains important both in the developed and in the developing countries. As to the disease classification, skin cancers have been divided into melanomas and non-melanoma skin cancers. They differ in the biological behavior and in the incidence. Melanomas show basic features of malignancy both clinically and histopathologically, while non-melanoma skin cancers show rather-benign clinical course in spite of their pathological features are invasive and clearly malignant.[1-7] The incidence of melanomas varied, being higher in western countries and lower in Asia Pacific regions; it seems to depend

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on intrinsic (genetic/racial) and the extrinsic factors.[3-7] The non-melanoma skin cancers appear to be equally frequent in both areas, although the non-melanoma skin cancer in light complexion in sun-exposed area has ever demonstrated to occur at 50-100 times higher than pigmented people.[2, 6]

In Indonesia, according to nearly nation-wide data collected from 13 pathology laboratories by the National Cancer Registry (Pathology based) the non-melanoma skin cancer ranked the first among males and fourth among females in 1988-1992.[8] In 1988 the relative frequency was 11.79 and 6.23 (age standardized cancer ratio=ASCAR= 12.16 and 6.16) respectively. Similarly in 1992 the figures were 11.21 and 6.35 (ASCAR=10.99 and 6.62) respectively. The incidence of non-melanoma skin cancers has been attempted to be obtained based on a population-based cancer registry of 1985-1989 in Semarang, West Java.[9] The figures also showed high ranking, namely ranked the second among males (mean age standardized rate 6.62 per 100,000) and the third among females (mean age standardized rate 6.54 per 100,000). Histologically, basal cell carcinoma and squamous cell carcinoma were the most common types.

Some features of malignant melanoma and malignant epidermal tumors have been reported by several investigators i.e. Tjarta, Kanoko and Mangunkusumo.[10] Their study of 5-year period (1985-1989) in Jakarta, the biggest pathological laboratory, showed that malignant skin tumors were found 5.9% to 7.8% among all malignancy per year. Almost the half (43.9%) of the cases were squamous cell carcinomas, 32.9% were basal cell carcinomas, 10.7% were malignant melanoma, and the rest (13.4%) consisted of malignant adnexal tumors, soft tissue sarcomas, malignant limphoid tissues, undifferentiated carcinomas and malignant blood vessel tumors. The males to females ratio was 1.4 to 1. The peak age of the cases (27.1%) was on 50-59 years. The most frequent site of all skin tumors were on head and neck (58.5%), while the rest were on the extremities (27.1%).

The malignant melanomas were found 56.8% in males and 43.2% in females. The lesions were mostly located in the lower extremities, namely in 78.3% of females and 54.8% of females, mainly on the sole and heel. The geographic distribution was analyzed by comparing the cases in Jakarta and the cases originated from outside Jakarta (spread over the country), as a rough comparison between urban and rural areas. The frequency of cases with the lesions on the foot in the first area seemed to be lower than the second area (43.7% *versus* 60.0% in females and 44.4% *versus* 50.0% in males).

In Japan, the incidence varied from 0.1-0.3 per 100,000 for melanoma and 0.4-2.4 for non-melanoma skin cancer as reported in Cancer incidence in five continents, IARC 1976.[11] Recently, the non-melanoma skin cancer (NMSC), the basal cell carcinoma (BCC) and solar keratosis (SK) increased during the last 20 years. The prevalence rates of BCC and SK were 16.5 and 487.6 per 100,000 population as reported by Ichihashi.[12, 13] It is of interest that subjects with Japanese skin type I (burn easily, tan poorly) showed higher risk for NMSC. The prevalence of SK of outdoor workers was higher than indoor ones.

The above mentioned information on skin cancer were very interesting. However, further analysis in respect to related factors needs further epidemiological study.

Simultaneous study comprising of epidemiological, clinicopathological and molecular pathological characterization of skin cancer both of the Indonesian and Japanese patients would be very valuable, to allow the understanding on the effect of environmental factors and to develop related protective measures against deliterious sunlight.

The results of such studies are expected to have mutual and appreciable benefits in the development of cancer control program with a multidisciplinary approach.

The study has been initiated by pilot studies performed both in Indonesian and in Japan, supported by local grants respectively. The definitive study has been supported by a three-year grant No. 09042004 (April 1, 1997 to March 31, 2000) under the auspices of the Ministry of Education, Science, Sports and Culture, the Government of Japan. It has been partly supported by the grants provided by the Indonesian Cancer Foundation, the Jakarta International Cancer Conference Fund and the Terry Fox Foundation, Canada.

The preliminary results have been discussed in the one day symposium and the details are published in the present monograph. The present paper will describe the planning and implementation of the collaborative study by taking into consideration the application of 5 phases of project management with adjustment to research project.

PLANNING OF THE COLLABORATIVE PROJECT

Further consideration for skin cancer study

Further studies of both melanoma and non-melanoma skin cancers remain important and interesting since the pattern of the diseases in both countries might show certain differences. The studies are aimed to analyze both the similarities and dissimilarities in several aspects, with specific interest on both intrinsic/genetic factors and extrinsic factors. The genetic factors would be related to the heterogeneity of the ethnic groups in Indonesia, while the extrinsic factors would be related to the variety/ degree of the exposure to carcinogenic agents (physical e.g. ultra violet of the sun rays or biological e.g. viruses). It can be anticipated that there might be specific or unique parameter discovered to be new findings in cancer research. Recent interest on molecular biological/ molecular pathological studies dealing with onco-genes and anti-oncogenes or tumor suppressor genes have been considered to elucidate further the biological behaviors of skin cancers.

The arrangement of the collaborative project has been organized according to 5-phases of project management, consisting of 2 phases of planning (defining and planning) and 3 phases of implementation (organizing, management/controlling and terminating),[14] with some modifications as to adjust to similar guidance[15, 16] and to fit to specific research project.[17, 18]

Preliminary discussion on the planning of the collaborative project has been initiated by the visit of Prof. Masamitsu Ichihashi, Dept. of Dermatology, Kobe University School of Medicine, on August 16-18th 1993, and the visit of Prof. Yoshiyuki Ohno, Dept. of Preventive Medicine, Nagoya University School of Medicine, on September 6-9th 1993, with the Indonesian team: Prof. Achmad Tjarta and Drs. Mpu Kanoko and Santoso Cornain. Further discussions were performed between Prof. Ohno and the whole Indonesian team mentioned above during his visit in January, June and September 1994.

Areas/ topic of studies have been discussed by both parties and the proposed studies and the organization of the study as a Multicenter Study are given in the addendum.

The already existing Scientific Working Group on Skin Cancer at the Faculty of Medicine University of Indonesia has been considered to be a strong support to the implementation of the collaborative project. Additional support was due to the fact that the research on oncology has been the top priority of the Research Program of the Faculty of Medicine.

Establishment of collaborative teams

In order to work further with the collaborative project, teams of both the Japanese and Indonesian sides were established as follows:

Japanese team: 1) Coordinator: Prof. Masamitsu Ichihashi MD, PhD (Dermatologist), Department of Dermatology, Kobe University School of Medicine, Kobe; 2) Prof. Yoshiyuki Ohno (Epidemiologist, Nagoya University School of Medicine, Nagoya), Ass. Prof. Masato Ueda (Dermatologist, Kobe University School of Medicine, Kobe), Prof. Kaoru Nonaka (Dermatologist, Ryuku University School of Medicine. Ryuku), Ass. Prof. Takashi Horikoshi (Dermatologist, Sapporo Medical College, Sapporo), Prof. Osamu Nikaido (Molecular Biologist, Kanazawa University, Kanazawa), Dr. Nobuo Munakata (Physicist, National Cancer Center Research Institute, Tokyo).

Indonesian Team: 1) Coordinator: Santoso Cornain, MD, DSc (Tumor Biologist, Immuno-pathologist), Department of Anatomic Pathology, Faculty of Medicine University of Indonesia, Jakarta; 2) Members: Mochtar Hamzah, MD (Dermatologist), Herman Cipto, MD (Dermatologist), Prof. Achmad Tjarta, MD (Pathologist), Mpu Kanoko, MD, PhD (Pathologist), Evert Poetiray, MD (Tumor Surgeon), Joedo Prihartono, MD, MPH (Epidemiologist), Santoso Cornain, MD, DSc (Tumor Biologist, Immunopathologist), Setyawati Budinigsih, MD, MPH (Epidemiologist), Dhanasari, MD (Epidemiologist).

Further team building was carried out by the coordinators, who functions as the linker among their respective members and between Indonesian and Japan. Further establishment of the collaborative project discussed in the periodic, 3-4 times per year, consultation meetings between Japanese and Indonesian teams.

Designing and writing research proposal

Both teams discussed the details of the research problems, the design and methodology which will be included in the term of reference for the collaborative study. The elaboration of the plan of study was

written in the proposal which is officially approved by the coordinators and the Dean.

The area/topic of studies were defined in two parts. The first part dealt with three fold study including epidemiological, clinical and histopathological aspects of skin cancer, while the second part dealt with study on tumor biology and molecular pathological aspects of skin cancer. Such definition was made to allow overall analysis of the data in relation to the main design of epidemiological study using a case-control method for the first part, while the data of the second part would be important for clarifying both the tumor biology and the molecular epidemiology of skin cancer. Comparative study on clinicopathology and various risk factors, i.e. constitutional/biological demographical/ethnical and environmental in particular sun exposure will be compared to earlier studies.[1-7, 12] Various molecular pathological markers including immunological, growth fraction, oncogenes and tumor suppressor genes, will be analyzed in respect to biological behavior and prognosis.[19-22]

Objective measurement of solar uv-B (ultraviolet-B) was planned in weekly and monthly exposure of spore-dosimeter at Jakarta and Denpasar, to be compared to Tokyo and other places.[23-24]

IMPLEMENTATION OF RESEARCH PROJECT

Organizing the project

The arrangements of the collaborative study were made in relation to the scheduling and assignment of the tasks, according to Gannt Chart system and Work Breakdown Structure or Flowchart. See Figures 1 & 2. Standard forms were developed for clinical study (A), Histopathological study (B) and Epidemiological questionnaires (C), accompanied with its manual for interviewer as given in Appendices 1-4.

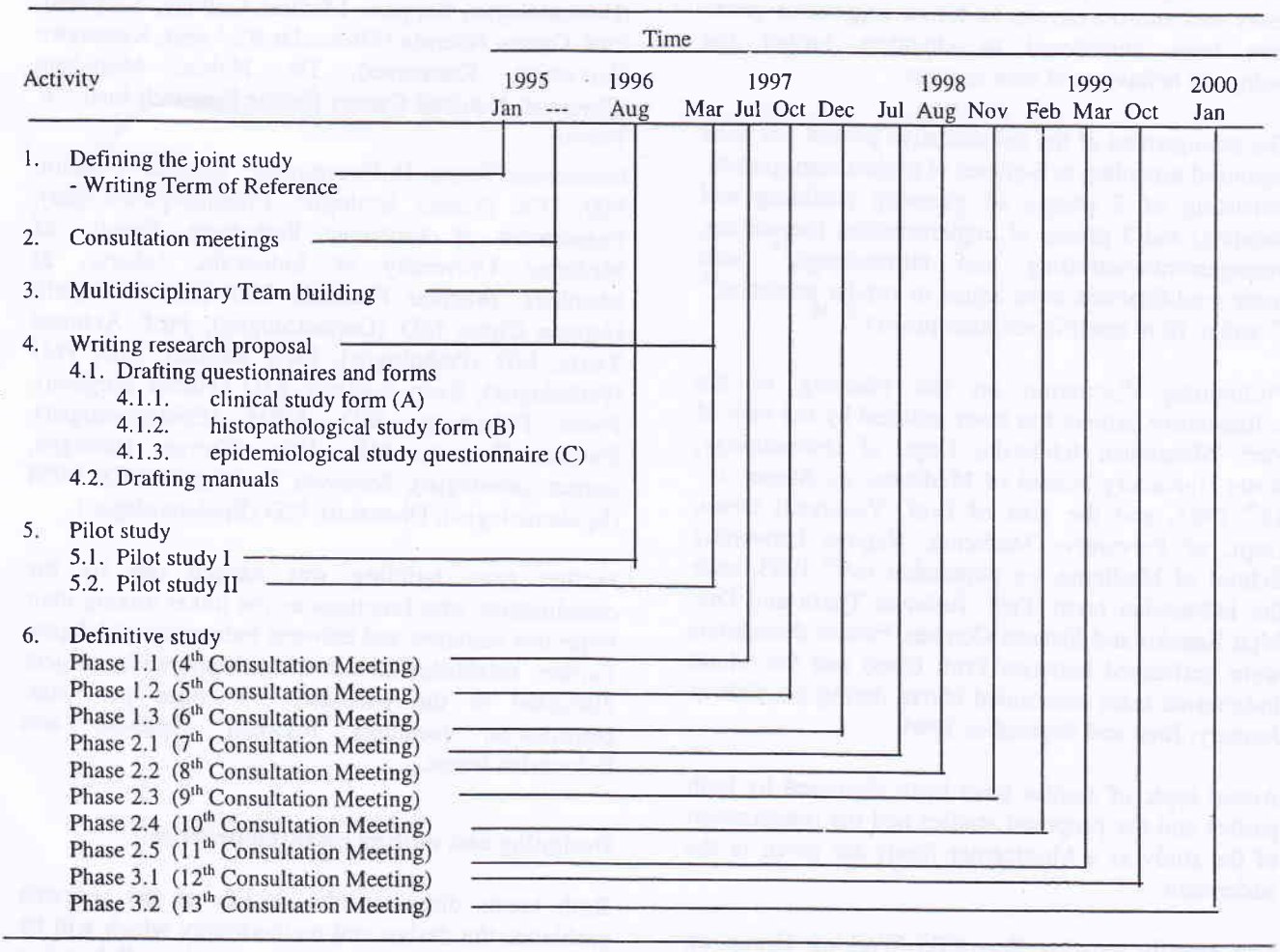

Figure 1. Gannt Chart of Schedules of Activities

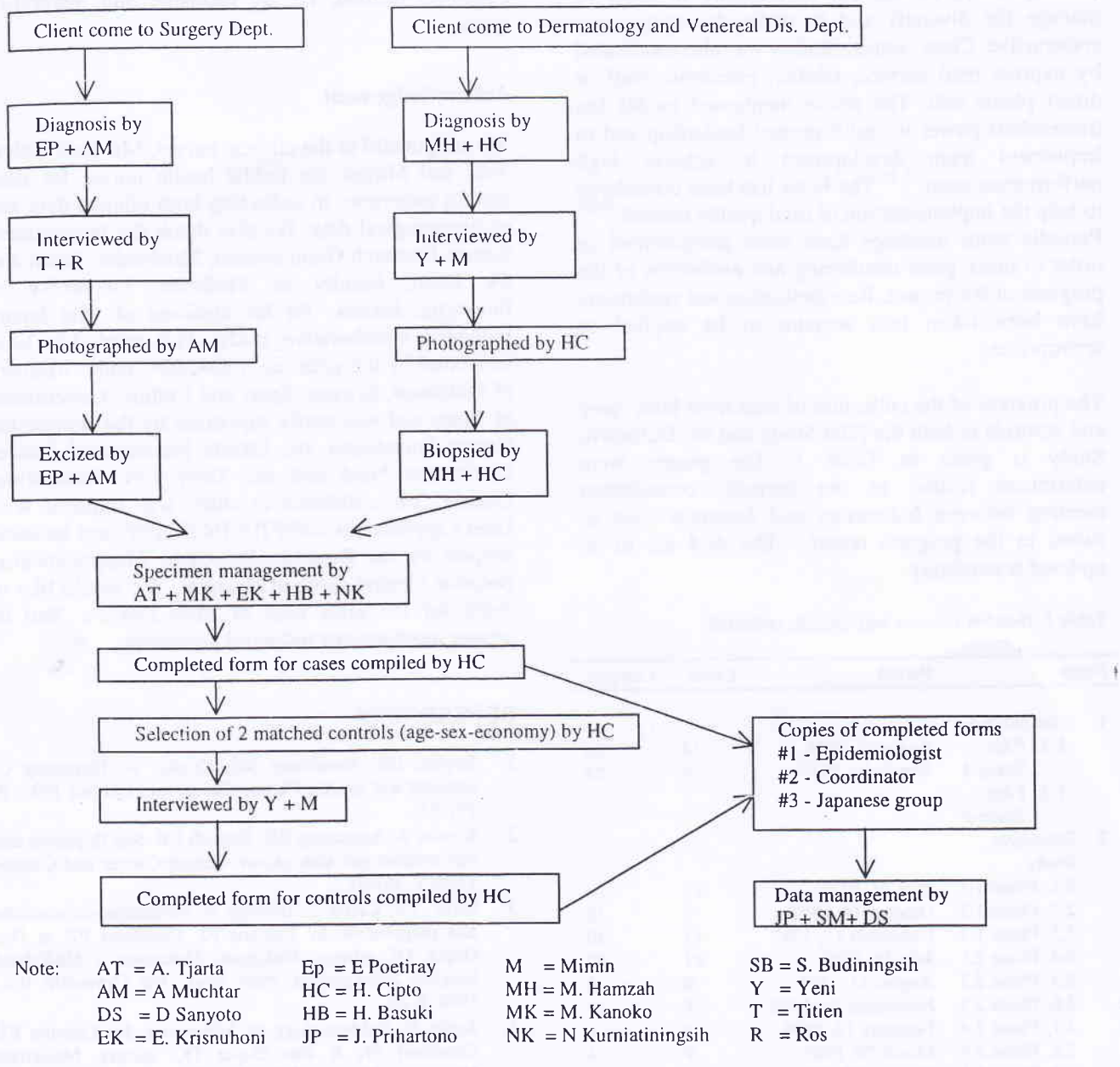

Figure. 2. Flow chart for Data management of Collaborative Case Control Skin Cancer Study

Various activities listed in the Gannt Chart were planned and made working in respect to the agreement of scheduling in the consultation meetings. The management of data collection was arranged by applying the Flow Chart, which made up a control system for ensuring the completeness and reliability of data collection. For expanding the coverage, in terms of larger number of data and both geographical area and ethnic groups, a multicenter study has been designed. The overall organizational structure includes all 13 university centers across the country. However, stepwise procedure was adopted for the implementation phase, i.e. 6 centers during the first phase. See Appendix 5.

Management and controlling of the project

The control system allows regular communications among the team members and immediate evaluations

of the progress of the study. Both informal and formal meetings were carried out periodically in order to manage the diversity and to make the controversy constructive. Close communication was also established by express mail service, telefax, electronic mail or direct phone call. The above mentioned model has tremendous power to instill project leadership and to implement team development to achieve high performance team.[16-25] The latter has been considered to help the implementation of total quality control.[26-27] Periodic team meetings have been programmed in order to make good monitoring and evaluation of the progress of the project. Reorganization and replanning have been taken into account to be applied as appropriate.

The progress of the collection of data from both cases and controls in both the Pilot Study and the Definitive Study is given in Table 1. The phases were determined related to the periodic consultation meeting between Indonesian and Japanese team as suited to the progress report. The data are to be updated accordingly.

Table 1. Number of cases and controls collected.

Phase	Period	Cases	Controls
1. Pilot Study-1			
1.1. Pilot Study-1	August 5, 1996	14	26
	March 10, 1997	14	28
1.2. Pilot Study-2			
2. Definitive Study			
2.1. Phase 1.1	July 29, 1997	13	20
2.2. Phase 1.2	October 14, 1997	9	18
2.3. Phase 1.3	December 15, 1997	11	20
2.4. Phase 2.1	July 28, 1998	41	80
2.5. Phase 2.2	August 31, 1998	6	6
2.6. Phase 2.3	November 31, 1998	18	34
2.7. Phase 2.4	February 12, 1999	4	6
2.8. Phase 2.5	March 29, 1999	9	4
2.9. Phase 3.1	October 27, 1999	26	46
2.10.Phase 3.2	January 24, 2000	16	24
	Total:	181	312

Terminating phase of the project

In anticipating the completion of the project by the end of the planned period, necessary changes were made including organization of data collection, data analysis, team working and funding system. The termination of the project will be arranged in combines method, i.e. by inclusion and integration types.

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