

UNDP/WORLD BANK/WHO
Special Programme for Research and Training in Tropical Diseases
(TDR)

Proposed Programme Budget
for the 1992-93 Biennium and
Estimates for 1994-95

ABBREVIATIONS AND ACRONYMS

BCV	Biological Control of Vectors Component
CHEMAL	Chemotherapy of Malaria Component
DIF	Director's Initiative Fund
EFR	Epidemiology and Field Research Support Component
FIELDMAL	Applied Field Research in Malaria Component
FIELDLINCS	Field Links for Intervention and Control Studies
GS	General Service Staff
IMMLEP	Immunology of Leprosy
JCB	Joint Coordinating Board
M	Million
MISTR	Management Information System of TDR
OCF	Onchocerciasis Control Programme in West Africa
OCT	Onchocerciasis Chemotherapy Project
P	Professional Staff
PDU	Product Development Unit
RSG	Research Strengthening Group
SER	Social and Economic Research Component
SFR	Swiss Franc
STAC	Scientific and Technical Advisory Committee
SWG	Scientific Working Group
TDR	Special Programme for Research and Training in Tropical Diseases
THELEP	Chemotherapy of Leprosy
UNDP	United Nations Development Programme
WHO	World Health Organization

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EXECUTIVE SUMMARY

The UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) was established in 1975 to undertake research and development for new and improved tools to control six major groups of tropical diseases and to strengthen the research capabilities of tropical countries in which these diseases are endemic. TDR's technical and administrative bodies guide and review the Programme's scientific and technical activities and provide support for its administrative and financial requirements (Sections 1.1, 1.2 and 1.3).

The major programme thrust and priority for 1992-93 is product development - the process of transforming basic scientific knowledge into usable disease control products. The newly-established Product Development Unit (PDU) will play a major role in this process, both providing expertise and serving as a focal point for product development throughout the Programme, and having direct responsibility for selected products. Resources for the PDU, including personnel, have been obtained from existing resources in the Programme, which will result in a significant readjustment of priorities. Other initiatives include combined chemotherapy development for African trypanosomiasis, Chagas disease and leishmaniasis, molecular approaches to mosquito vector control, and operational research on drug distribution. Malaria remains the most important of the TDR target diseases, and relatively greater emphasis is also placed on social and economic research. There are decreases in some components, such as leprosy and African trypanosomiasis, in view of the changing epidemiological situation and the development of new control tools for these diseases. The previous two components for leprosy, Chemotherapy of Leprosy and Immunology of Leprosy, have been combined into a single component in the light of changing priorities and workload (Section 1.4).

The Programme Budget proposed for 1992-93 is US\$ 76 845 000, an increase of US\$ 3 921 700 or 5.4 per cent over the Revised Budget for 1990-91. In the light of anticipated funds available in the biennium, it is unlikely that the continued rapid financial growth of recent years can be sustained. In constant dollar terms, TDR's actual expenditures are about the same level now as they were in the early 1980s. The decline in value of the US dollar in terms of other major currencies has meant an increase in the dollar value of some contributions to the Programme, but also major cost increases, especially for personnel. Contributions required to finance the Programme Budget for 1992-93 will be about US\$ 71.2 million, US\$ 6.8 million more than anticipated contributions in 1990-91. About 24.9 per cent of the proposed budget will be devoted to Research Capability Strengthening. The overall per cent devoted to Programme Operations will be 73.1 (Section 2).

Separate texts for each of the thirteen research and development components in Programme Area II present the objectives, planned activities and proposed budget for each component (Section 4). The new Product Development Component will receive US\$ 6 970 000, including staff costs and operational support. An initial list of priorities for product development is contained in Figure 7 (Section 4.2).

Within Research Capability Strengthening (Programme Area III), greater emphasis will be placed on training activities and new measures will be undertaken to provide support for least developed countries. Major recent undertakings such as the TDR-Rockefeller Foundation Joint Programme and programme-based grants will be evaluated. Support for field research, especially through the Field Links for Intervention and Control Studies (FIELDLINGS) project, will continue to be a priority (Section 5).

Programme Management (Programme Area IV) shows some savings of resources, especially personnel, resulting largely from streamlined procedures and efficiency gains resulting from the increased use of computers, especially microcomputers, and new computer-based systems. The previous arrangements whereby five regional offices of WHO contributed to TDR and TDR provided posts in the regional offices have been discontinued (Section 6).

The Programme Budget for 1992-93 contains 132 proposed staff years (66 posts), a reduction of 30 staff years (15 posts) from the 1990-91 budget. Twenty of the staff years (10 posts) represent the transfer of the posts in the regional offices of WHO and the remaining 10 staff years (5 posts) are reductions in TDR headquarters staff, resulting mainly from gains in efficiency. The posts assigned to the Product Development Component have been drawn from a number of components (Section 7).

TABLE 1 Budget Summary (US\$000 and Per Cent)

PROGRAMME AREA/COMPONENT	1990-1991		1992-1993		1994-95	
	(1) APPROVED BUDGET	(2) REVISED BUDGET	(3) PROPOSED BUDGET	(4) INCREASE/(DECREASE) (3)-(2)	(5) PER CENT	(6) ESTIMATED
I Technical and Administrative Bodies	645.0	620.0	650.0	30.0	4.8	700.0
--Per cent of Total	0.9	0.9	0.8	0.8		0.8
II Research and Development						
General Activities	1,342.5	1,105.0	1,190.0	85.0	7.7	1,300.0
Director's Initiative Fund	1,500.0	750.0 *	1,500.0	750.0	100.0	1,700.0
Product Development	-	-	6,970.0	6,970.0	-	7,700.0
Chemotherapy of Malaria	6,025.5	6,290.0	6,300.0	10.0	0.2	6,900.0
Immunology of Malaria	5,575.0	5,335.0	5,050.0	(285.0)	(5.3)	5,600.0
Applied Field Research in Malaria	3,500.0	4,075.0	3,950.0	(125.0)	(3.1)	4,300.0
Schistosomiasis	3,000.0	3,290.0	2,650.0	(640.0)	(19.5)	2,900.0
Filariasis	4,775.0	4,475.0	4,200.0	(275.0)	(6.1)	4,600.0
African Trypanosomiasis	3,300.0	3,330.0	2,540.0	(790.0)	(23.7)	2,800.0
Chagas Disease	2,600.0	2,690.0	2,365.0	(325.0)	(12.1)	2,600.0
Leishmaniasis	3,000.0	3,186.0	2,950.0	(236.0)	(7.4)	3,200.0
Leprosy	6,600.0	5,960.0	4,600.0	(1,360.0)	(22.8)	5,100.0
Biological Control of Vectors	2,300.0	2,400.0	2,350.0	(50.0)	(2.1)	2,600.0
Social and Economic Research	2,525.5	3,015.0	3,040.0	25.0	0.8	3,300.0
Subtotal-Programme Area II	46,043.5	45,901.0	49,655.0	3,754.0	8.2	54,600.0
--Per cent of Total	63.1	62.9	64.6	95.7		64.7
III Research Capability Strengthening						
General Activities	2,255.2	2,045.0	1,760.0	(285.0)	(13.9)	1,900.0
Institution Strengthening	8,300.0	6,250.0	6,200.0	(50.0)	(0.8)	6,800.0
Training	5,700.0	7,850.0	9,250.0	1,400.0	17.8	10,200.0
Epidemiology and Field Research	2,650.0	2,125.0	1,940.0	(185.0)	(8.7)	2,100.0
Subtotal-Programme Area III	18,905.2	18,270.0	19,150.0	880.0	4.8	21,000.0
--Per cent of Total	25.9	25.1	24.9	22.4		24.9
IV Programme Management						
Personnel	3,456.2	3,950.0	4,130.0	180.0	4.6	4,500.0
Operational Support	700.0	780.0	650.0	(130.0)	(16.7)	700.0
General Support	2,138.0	2,350.0	2,610.0	260.0	11.1	2,900.0
Regional Offices	1,052.3	1,052.3	0.0	(1,052.3)	(100.0)	0.0
Subtotal-Programme Area IV	7,346.5	8,132.3	7,390.0	(742.3)	(9.1)	8,100.0
--Per cent of Total	10.1	11.2	9.6	(18.9)		9.6
GRAND TOTAL	72,940.2	72,923.3	76,845.0	3,921.7	5.4	84,400.0

* An amount of US\$ 750 000 was reallocated in 1990-91 from the Director's Initiative Fund to the operations budgets of other components (see also Section 4.1).

1. PROGRAMME OVERVIEW AND PRIORITIES

1.1 Objectives

The UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) was established in 1975 with two interdependent objectives:

- ° To develop new methods of preventing, diagnosing and treating selected tropical diseases, methods that would be applicable, acceptable and affordable by developing countries, require minimal skills or supervision and be readily integrated into the health services of these countries;
- ° To strengthen - through training in biomedical and social sciences and through support to institutions - the capability of developing endemic countries to undertake the research required to develop these new disease control technologies.

TDR's activities are targeted towards six disease groups: malaria, schistosomiasis, filariasis (including onchocerciasis or river blindness), the trypanosomiasis, (both African sleeping sickness and the American form, Chagas disease), the leishmaniasis and leprosy.

1.2 Structure

The Special Programme is co-sponsored by the United Nations Development Programme (UNDP), the World Bank, and the World Health Organization (WHO), with WHO as the Executing Agency. The Memorandum of Understanding on the Administrative and Technical Structures of the Special Programme (1978; amended 1988) describes the functions, composition and operation of the Programme's principal management bodies. TDR's structure includes the following scientific and administrative bodies (see also Figure 1.):

Joint Coordinating Board (JCB) - The JCB, TDR's senior management body, meets annually to review TDR activities, consider long-term plans, determine the budget and evaluate progress. The 30 members of the JCB include representatives of 12 governments selected by financial contributors to the Programme, 12 governments of countries affected by TDR's target diseases, or countries providing technical or scientific support to the Programme, three governments or agencies selected by the JCB itself and the three co-sponsoring agencies.

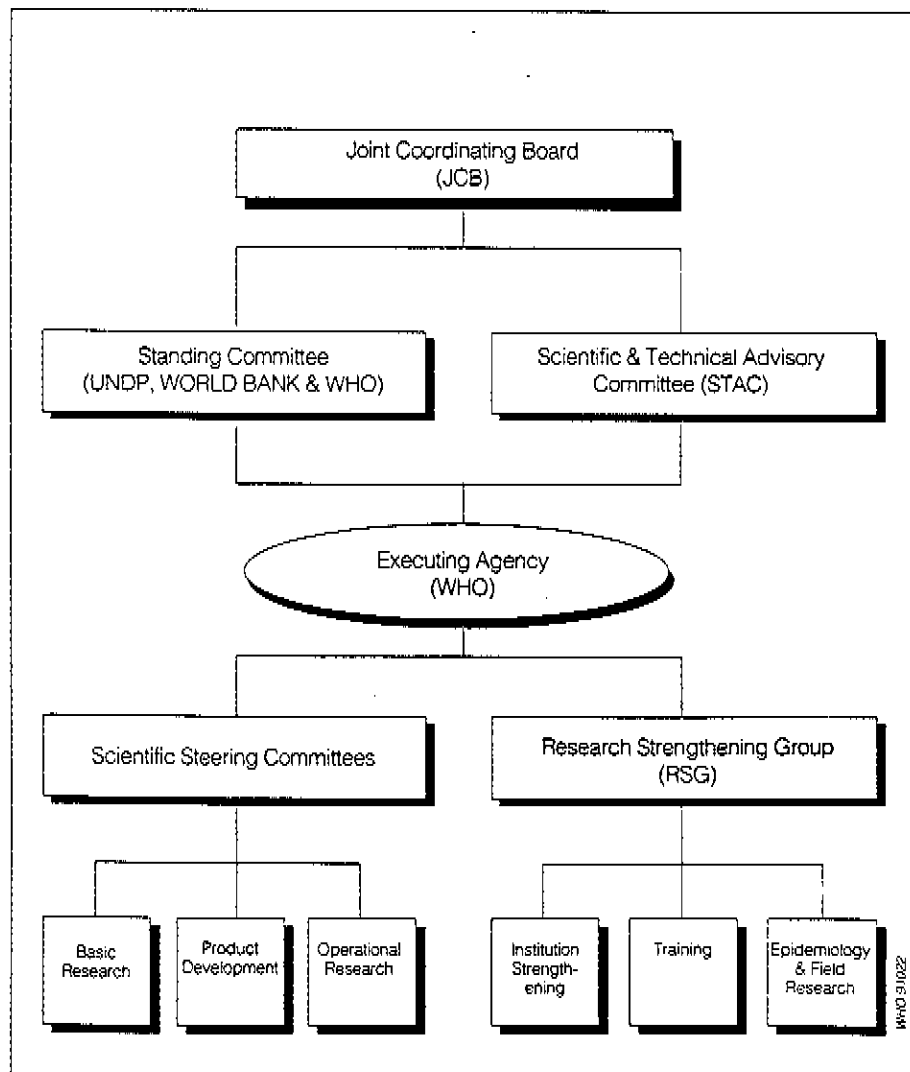
Scientific and Technical Advisory Committee (STAC) - STAC, composed of 15 to 18 experts from a wide range of scientific disciplines, acts as technical adviser to both the JCB and the Programme secretariat. It reviews the Programme's scientific activities and reports its findings to the JCB. Detailed evaluations of TDR components and of trans-disease aspects of the Programme are carried out by scientific and technical reviews by committees which include STAC members and other experts.

Standing Committee - Representatives of the three co-sponsors meet three times a year as the Standing Committee to oversee the overall management and financing of the Programme.

Scientific Steering Committees - TDR's research and development activities are organized on the basis of Components which are established by STAC for each of TDR's target diseases. Trans-disease Components for social and economic research and for biological control of vectors deal with disciplines important to several diseases. Research and development activities are managed through *Scientific Steering Committees*, which meet at least once a year to prepare research plans, assess research proposals and review scientific progress. *Scientific Working Groups* bring together scientists involved in TDR activities to make periodic state-of-the-art reviews and elaborate new strategies in specific areas.

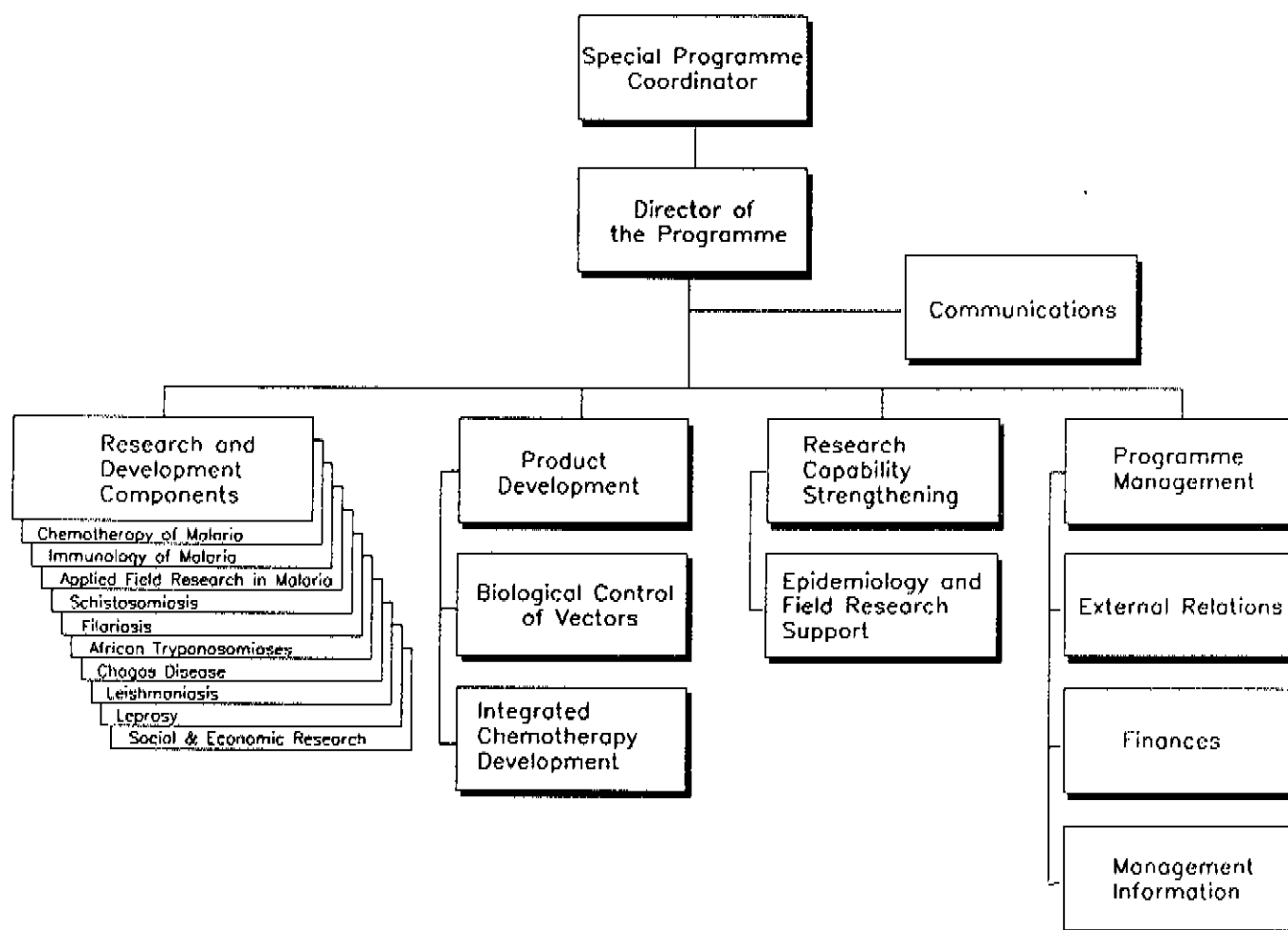
Research Strengthening Group (RSG) - Major responsibility for implementing TDR's efforts to strengthen the research capabilities of tropical countries rests with the RSG. Its 12 to 15 members, selected for their experience in research management and training in developing countries, prepare overall plans, review proposals for research strengthening, consider applications for research training and evaluate progress.

FIGURE 1 TDR's Technical and Administrative Bodies



The organization of the Programme Secretariat within WHO is shown in Figure 2. The Special Programme Coordinator, who is normally an Assistant Director-General of WHO, is responsible for the overall coordination of TDR within the Organization, including liaison with WHO senior management. The Director of the Special Programme has executive responsibility for planning, organizing and implementing TDR's activities within the framework of the Memorandum of Understanding on the Administrative and Technical Structures of the Special Programme, and decisions and recommendations of the Joint Coordinating Board, the Scientific and Technical Advisory Committee and the Standing Committee. The Director is supported by a small staff and the Communications Unit. Programme activities are carried out by research and development components, each of which consists of a Steering Committee supported by a professional staff member, the Secretary to the Steering Committee. The Product Development Unit provides leadership and expertise for product development throughout the Programme and has direct responsibility for the advancement of selected products (see also Sections 1.4 and 4.2). In addition, the Unit supervises the Biological Control of Vectors Component and Integrated Chemotherapy Development. Research Capability Strengthening, which also includes Epidemiology and Field Research Support, implements the Programme's activities in institution strengthening, training, epidemiology and field research. Programme Management provides external relations and support for administrative and financial management of all TDR activities.

FIGURE 2 Organization of the Programme Secretariat



Coordination of TDR's activities with other WHO programmes responsible for assisting Member States to improve their disease control activities is reinforced through a matrix organization approach. The Secretaries of the TDR Steering Committees are co-located with the relevant WHO disease control personnel in the Division of Control of Tropical Diseases (CTD), providing for constant interchange between research and control activities. Regular communications and cooperative efforts also link TDR's research and development and research capability strengthening and training activities to WHO's other special and global programmes, especially the Special Programme of Research, Development and Research Training in Human Reproduction (HRP), the Division of Diarrhoeal and Acute Respiratory Diseases Control (CDR), the Expanded Programme on Immunization (EPI), and the Global Programme on AIDS (GPA). TDR's activities are also closely coordinated with those of the Division of Drug Management and Policies (DMP), the Division of Development of Human Resources for Health (HRH) and the Applied Vaccinology Programme in the Division of Communicable Diseases (CDS).

1.3 Targets

TDR's general targets for the period 1990-95, contained in the WHO *Eighth General Programme of Work 1990-95*, are as follows:

- (1) Goal oriented research and development, aiming to achieve:
 - field application or advanced clinical trials of improved or new chemotherapeutic agents for at least three of the six diseases;

- ° field applications or assessment of large-scale trials of a candidate leprosy vaccine, advanced trials of one or more possible malaria and schistosomiasis vaccines, and field application or advanced trials of one or more vaccines against cutaneous leishmaniasis;
 - ° field application or advanced trials of new simple tests and micro-techniques for diagnosing disease and for monitoring drug susceptibility;
 - ° field application or advanced trials of two or more new biological agents for the control of disease vectors; and
 - ° establishment of the epidemiological, social and economic bases for the development of more effective national strategies for the integrated control of six diseases.
- (2) Through the strengthening of national institutions of the tropical countries affected by the diseases, the Programme will assist in developing:
- ° a network of 80 to 100 self-reliant national research and training centres, and technical collaboration among developing countries for research careers in their home countries.

1.4 Major Programme Thrusts and Priorities

TDR's activities span a broad range from basic research on the target diseases, the parasites and vectors, to operational or health systems research aimed at learning how disease control products can be utilized most effectively and efficiently. Between these two is product development, the process of transforming basic scientific knowledge into usable disease control products, including pre-clinical and clinical evaluations of these products, to the stage of registration or other form of licensing for utilization. In the initial years of the Programme, considerable emphasis was placed on basic research, to improve knowledge about fundamental aspects of the diseases, such as incidence, parasite metabolism and mechanisms of immunity, vector life cycles and distribution and resistance of the disease organisms to drugs. From these efforts, as well as from general advances in biomedical research, came ideas for new vaccines, drugs, diagnostics and vector control methods - TDR's "products".

Many potential products supported by TDR are ready to move from primarily laboratory-based research to intensive development prior to large-scale trials in disease endemic countries. TDR is in fact involved in the development of more products than many medium-sized pharmaceutical companies. Because of high cost and complexity of product development, TDR cannot undertake the simultaneous development of all or even most of the potential products which have been supported in early stages. Clear priorities must be made and the development of the selected high priority products pursued on an urgent basis. Product development is the highest priority of the Programme at the present time.

The importance of product development was recognized by the Scientific and Technical Advisory Committee and the Joint Coordinating Board at their meetings in 1990. Acting on the recommendation of STAC, the JCB agreed on the establishment of a Product Development Unit within TDR, based on existing resources, to undertake the development of high priority products. The Board requested that detailed proposals for the operations of the Unit be presented to the Board in the Proposed Programme Budget for the 1992-93 Biennium.

In approving the establishment of the Product Development Unit, the Board emphasized the need to promote product development in developing countries and noted that the Unit would facilitate and stimulate increased collaboration with industry and assist in bridging gaps in the development of products crucial to tropical disease control.

Proposals for the initial activities of the Product Development Unit (PDU) are contained in Section 4.2, together with a table summarizing initial product development priorities. In addition to providing expertise and serving as a focal point for product development in the Programme as a whole,

the Unit will have direct responsibility for selected products, in collaboration with the component concerned. Not all product development activities can be concentrated in the Unit: the disease components will continue to be responsible for the development of many products, with the assistance of the PDU.

The proposed operations budget (US\$ 4.5 million) for Product Development has required a significant re-ordering of priorities within the Programme. The Scientific and Technical Advisory Committee conducted a careful review of overall programme priorities at its Thirteenth Meeting in March 1991 (see also Report of the Thirteenth Meeting of the Scientific and Technical Advisory Committee (STAC-13), document TDR/STAC-13/91.3). On the basis of this review, the malaria, filariasis and leishmaniasis components, together with Social and Economic Research and Biological Control of Vectors, receive greater priority than the components for schistosomiasis, African trypanosomiasis, Chagas disease and leprosy.

The amounts recommended by STAC for operations are contained in the separate tables for each component in Research and Development (Sections 4.1 to 4.13) and Research Capability Strengthening (Sections 5 and 5.1). The operations budget for Chemotherapy of Malaria has been increased to take account of designated funding for a project on the development of antimalarial drugs based on *Artemisia annua* (see Section 4.3).

Other initiatives recommended by the Scientific and Technical Advisory Committee in 1990 were the linking of research for new drugs against African trypanosomiasis, Chagas disease and leishmaniasis, the exploration of molecular approaches to mosquito vector control, and research aimed at increasing the effectiveness of distribution of drugs against TDR target diseases. Planning for these initiatives was carried out in 1990 and some activities are already underway in 1991. Responsibility for the integrated approach to drug development for African trypanosomiasis, Chagas disease and leishmaniasis has been assigned to the Product Development Unit and a separate operations budget item will be established in the Product Development Component (see Section 4.2).

The initiative for molecular approaches to mosquito vector control is being undertaken in close collaboration with other interested institutions, such as the John D. and Catherine T. MacArthur Foundation and the Wellcome Trust, and it is anticipated that TDR will play a key role in supporting research in developing country laboratories, including the provision of training and institution strengthening. This initiative will be carried out by the Biological Control of Vectors Component (see Section 4.12).

Questions related to the effectiveness of distribution of drugs for tropical diseases are closely related to operational research on other aspects of tropical disease control. TDR is supporting research in this area through the Social and Economic Research Component, in close collaboration with the WHO Division of Control of Tropical Diseases (see Section 4.13). TDR is also supporting research aiming at reduced drug distribution costs by combining drug development for different diseases concomitantly through the Schistosomiasis Component.

Research Capability Strengthening, including Epidemiology and Field Research Support, continues to be a major priority of the Programme. Proposed allocations for Research Capability Strengthening are 24.9% of the total budget. Following several years of major innovations and modifications, such as the TDR-Rockefeller Foundation Joint Programme and programme-based grants, the 1990-91 biennium was characterized by a consolidation of existing programme mechanisms, measures to relate research capability strengthening more closely to TDR's research and development priorities and activities, and a review of the role of research training. As a result, training activities are more strongly emphasized and the Research Strengthening Group is actively involved in the selection of trainees. In addition, in cooperation with other WHO programmes, TDR is pursuing assistance in the least developed countries where activities have been minimal to date (see Section 5).

Field research, broadly defined to include research which involves the collection of primary data from individuals, their communities and/or their environments in developing countries, increases in importance as more disease control products developed with TDR support require field trials in disease endemic areas or enter into disease control use. Field research on particular disease control products is

supported under the various disease- and trans-disease components, while the Epidemiology and Field Research Support Component aims to improve capacity for conducting field research in developing countries. A major initiative is the Field Links for Intervention and Control Studies (FIELDLINGS) project, which aims to provide support for field-based investigators through multi-disciplinary networks (see Section 5.1).

Turning to priorities among the target diseases as reflected in budget allocations, malaria, the most important of the TDR target diseases, will receive US\$ 15.3 million or 35.8% of the proposed budget of US\$ 42.7 million for Research and Development, Programme Area II (to permit comparison with the budget for the 1990-91 biennium, the new Product Development Component is excluded from the per cent figures - see Table 1.1). This is a slight increase in the proportion allocated to malaria, which received 34.2% of the Research and Development budget in 1990-91. Social and Economic Research will also receive a larger share of the budget, increasing from 6.6% in 1990-91 to 7.1% in 1992-93, reflecting the importance of social and economic research at this stage in the Programme's development and an increased tempo of activities following an intensive effort to involve more developing country social scientists in tropical diseases. Biological Control of Vectors also increases slightly. Filariasis and leishmaniases will remain at about the proportion of the budget as previously, about 9.8% and 6.9% respectively.

Significant declines in budget allocations occur for leprosy and African trypanosomiasis, and smaller declines for schistosomiasis and Chagas disease. These declines are not based on a lower priority assigned to the diseases as such, but rather on the evolution of the epidemiological situation, especially in the case of leprosy, and on the development of new control tools, such as eflornithine for the treatment of African trypanosomiasis. The effective multi-drug therapies for leprosy are having a significant impact on the numbers of registered leprosy cases, which are diminishing for the first time. In this situation, TDR's priorities are the completion of the development and trials of the leprosy vaccines already under

TABLE 1.1 Budget Allocations to Target Diseases & Trans-disease Components, 1990-91 & 1992-93

Disease/Component	Revised	Proposed	Revised	Proposed
	Budget	Budget	Budget	Budget
	1990-91	1992-93	1990-91	1992-93
	(US\$000)	(US\$000)	(Per Cent)	(Per Cent)
General Activities	1 855.0	2 690.0	4.0	6.3
Malaria	15 700.0	15 300.0	34.2	35.8
Schistosomiasis	3 290.0	2 650.0	7.2	6.2
Filariasis	4 475.0	4 200.0	9.7	9.8
African Trypanosomiasis	3 330.0	2 540.0	7.3	6.0
Chagas Disease	2 690.0	2 365.0	5.9	5.5
Leishmaniases	3 186.0	2 950.0	6.9	6.9
Leprosy	5 960.0	4 600.0	13.0	10.8
Biological Control of Vectors	2 400.0	2 350.0	5.2	5.5
Social & Economic Research	3 015.0	3 040.0	6.6	7.1
Subtotal	45 901.0	42 685.0	100.0	100.0
Product Development	0.0	6,970.0		
TOTAL PROGRAMME AREA II	45 901.0	49 655.0		

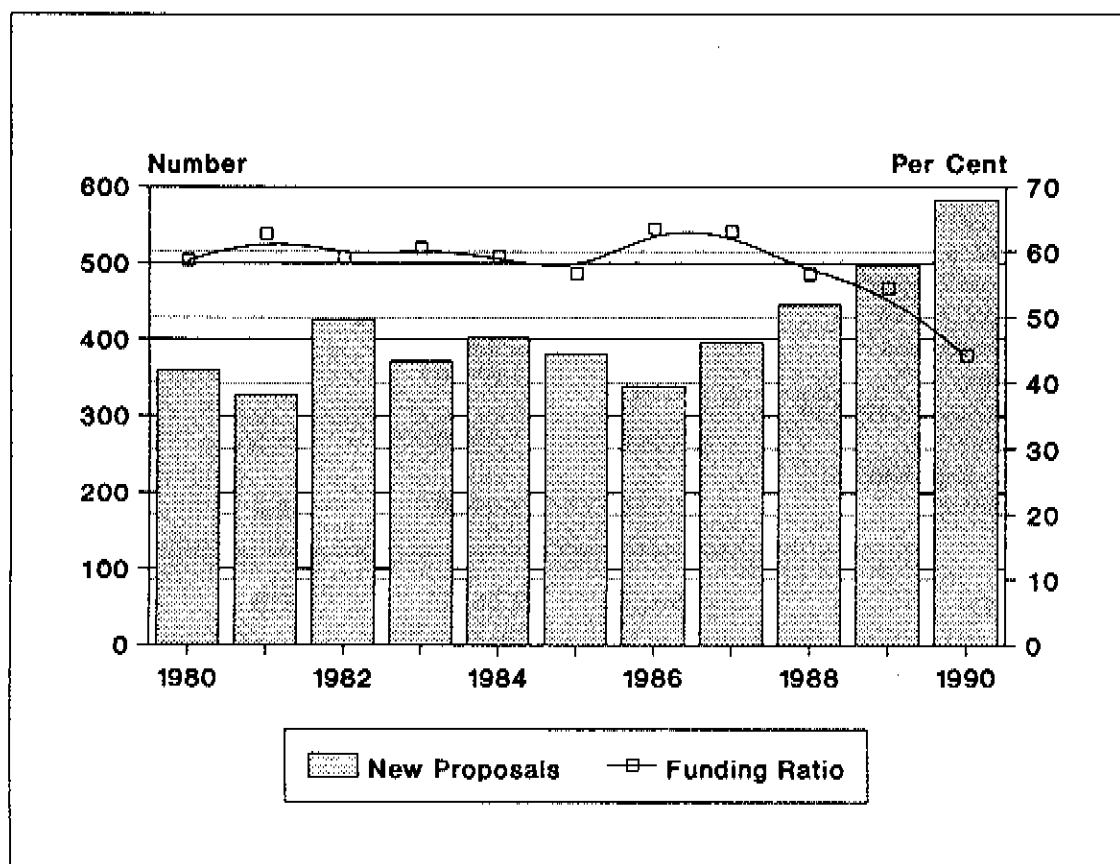
way, clinical trials of new anti-leprosy compounds already identified and operational research on the use of multi-drug therapies, especially in areas where utilization rates are low, such as many African countries. The compounds which are now entering clinical trials could result in even shorter duration therapy than the existing regimens and in the availability of effective replacement drugs should resistance begin to appear to the current drugs. Future financial requirements for these activities are considerably reduced from allocations in recent biennia and it has been decided to fuse the two previous components for leprosy, while retaining separate operations budgets for chemotherapy and for immunology (see Section 4.11).

The registration of eflornithine for the treatment of African trypanosomiasis is an important development in the treatment of this disease. Future priorities are focussed on more effective regimens of eflornithine, the development of other, more easily usable drugs and of simple and effective diagnostic tools. The search for new drugs will be undertaken in the context of the integrated drug development effort, which also reduces the financial requirements for the African Trypanosomiasis Component.

In schistosomiasis, greater priority will be given to the research for an effective vaccine and to multi-disease chemotherapy, with less emphasis placed on a number of other research areas, such as snail control. With the development of effective vector control tools for Chagas disease, future priorities will be new diagnostic tools and new methods for treatment of infected blood in blood banks. Chagas disease is also a target disease for the new integrated chemotherapy venture.

The number of new research and development proposals (Programme Area II) considered by the Programme has increased sharply in recent years, reaching 582 in 1990, an increase of 72% in four years (see Figure 3). This is a reflection of increased scientific interest in tropical disease research in both developing and industrial countries. The increase in the number of projects not only places a greater review and management burden on the Scientific Steering Committees and the Secretariat, but also results in greater "competition" for available funds. Accompanying the increased number of new research and development proposals has been a decrease in the "funding ratio" (the proportion of proposals funded to those funded or rejected), which fell from an average of 60.4% between 1980 and 1983, to 55.5% in 1988-89 and 44.1% in 1990 (see Figure 3).

FIGURE 3 Research and Development Project Proposals and Funding Ratio 1980-90



2. PROGRAMME BUDGET AND FINANCING

2.1 Budget Level

The Programme Budget proposed for the 1992-93 biennium is US\$ 76 845 000. This is US\$ 3 921 700 or 5.4% more than the revised budget of US\$ 72 923 300 for the 1990-91 biennium. The Proposed Budget reflects a reasonable assessment of Programme requirements balanced against estimates of financial resources likely to be available to TDR during the biennium.

The level of the Proposed Programme Budget is, however, considerably less than the estimated amount of US\$ 83 000 000 contained in the *TDR Programme Budget for the 1990-91 Biennium and Estimates for 1992-93*. The amount of US\$ 83 000 000 had been established on the basis of the recommendations of the Second External Review Committee of TDR, which concluded that in the period 1988-93, there would be a need for funding at least 25 to 30 per cent in real terms above the budget levels of 1988 (*Report of the Second External Review Committee*, TDR, 1988, p. 71). This recommendation was reflected in the level of the Programme Budget for 1990-91, but the continued rapid growth cannot be fully sustained in 1992-93, in light of expected availability of resources (see also Section 2.2).

Figure 4 shows the evolution of TDR contributions, obligations and budgets from 1976 to 1990, with projections for 1991 to 1993 (biennial budgets have been divided into two equal annual amounts in this Figure). All the amounts contained in this Figure are expressed in current dollars - the actual amounts in the year in question. Current dollar obligations actually declined from highs of US\$ 25.0 million and US\$ 25.1 million reached in 1980 and 1981, to US\$ 21.4 million in 1984 and US\$ 21.9 million in 1986. Since 1986 there has been a steady rise in the level of obligations, reaching an actual amount of US\$ 34.7 million in 1990 and a forecast level of US\$ 38.2 million in 1991. The proposed budget level of US\$ 76.8 million for 1992-93 results in an annual average rate of US\$ 38.4 million, about the same as the forecast obligations for 1991.

FIGURE 4 TDR Contributions, Obligations and Budgets 1976-93 (US\$M)

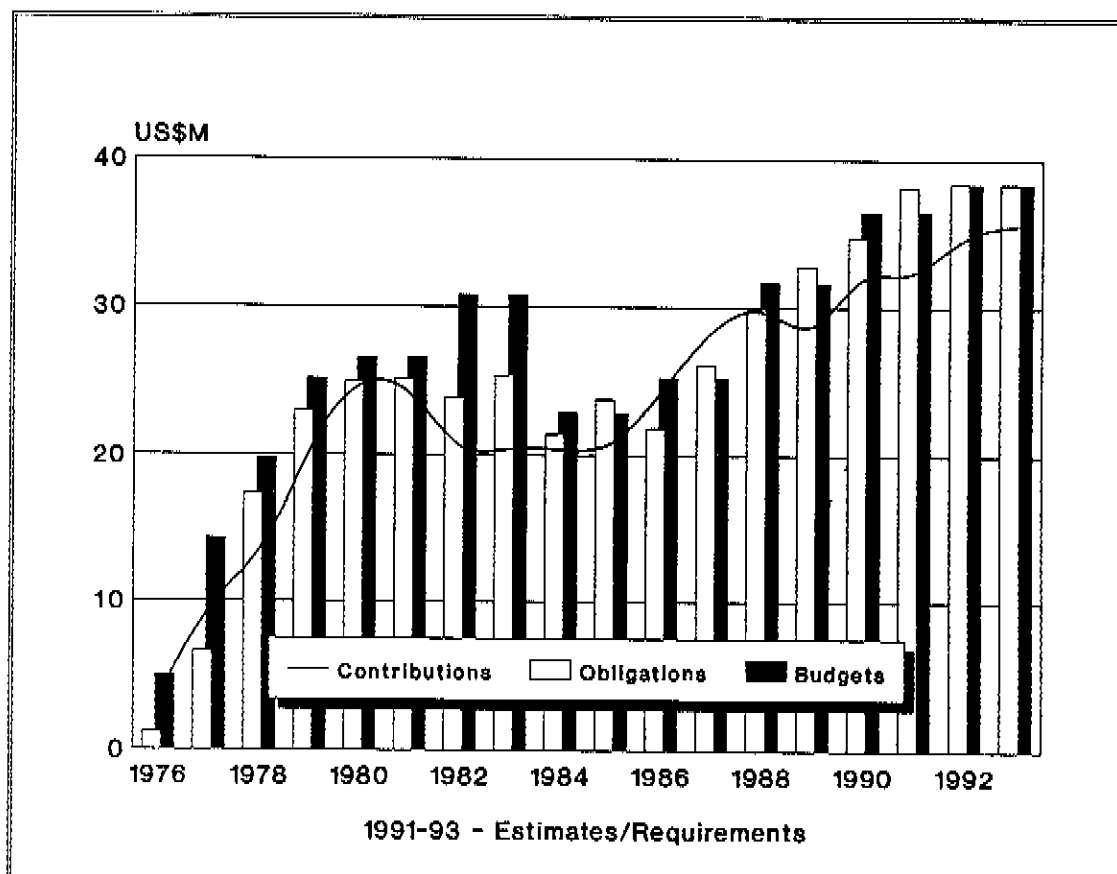


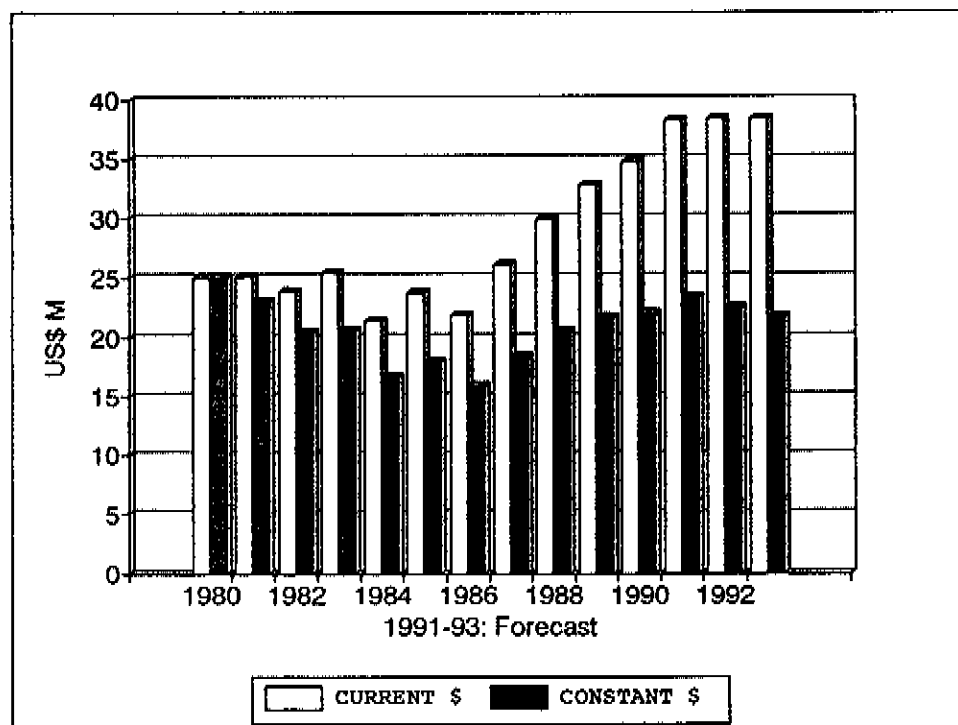
TABLE 2.1 GDP Deflator for Industrial Countries 1980 (Per Cent)

1980	1981	1982	1983	1984	1985	1986	1987	1988	1989
9.5	9.0	7.3	5.2	4.3	3.6	3.4	3.1	3.1	3.6

Source: IMF, *International Financial Statistics Yearbook 1990*.

The picture in constant dollars - dollars reduced by a suitable factor reflecting the loss in value over time - is quite different from that in current dollars. Figure 5 shows the evolution of TDR obligations from 1980 to 1990, with forecasts to 1993, expressed in both current dollars and constant 1980 dollars (the GDP deflator for industrial countries for the period 1980 to 1989 (Table 2.1) and an amount of 4 per cent per year for 1990 to 1993 have been utilized to derive constant dollar amounts in this Figure). The constant dollar figures show a much more dramatic decline after 1980, to a low point of US\$ 15.9 million 1980 dollars in 1986. The increases in obligations from 1987 have almost restored the real value of TDR obligations to the levels reached in the early 1980's - but the budget level proposed for 1992-93 again represents a decline in real value from the 1990-91 level.

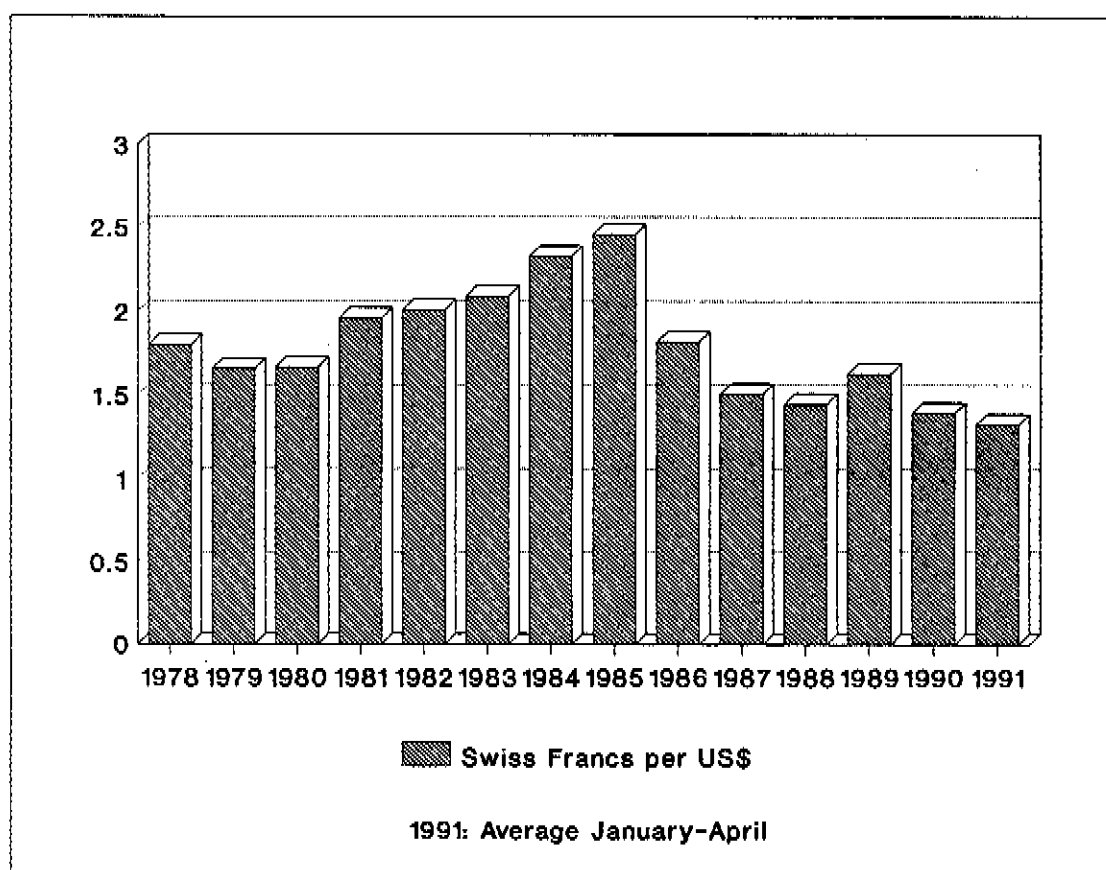
FIGURE 5 TDR Obligations 1980-93: Current and Constant US Dollars



In addition to erosion of value by inflation over the years, TDR's financial situation is also strongly affected by international currency fluctuations, especially variations in the value of the US dollar in relation to other major currencies. For TDR financial purposes, the most important exchange rate is the value of the US dollar in terms of Swiss francs. Figure 6 illustrates the fluctuation in the annual average of the official UN exchange rate for the Swiss franc between 1975 and 1990 and the first four months of 1991. From a high level of SFR 2.46 per US dollar in 1985, the dollar fell steadily, with a slight increase in 1989, to a low of SFR 1.40 in 1990. In the first four months of 1991, the dollar averaged SFR 1.33, with a sharp rise in April.

The decline in value of the US dollar relative to other major currencies, such as the Swiss franc (see Figure 6), has major effects on TDR's finances. The most significant immediate effect is that the US dollar value of contributions to TDR in a number of other currencies increases as the dollar declines. Between 1986 and 1988, for example, about 63 per cent of the increases in contributions over 1985 from 16 major contributors, expressed in US dollars, could be attributed to exchange rate gains as a consequence of the decline of the US dollar relative to other major currencies. The sensitivity of TDR income to exchange rate fluctuations is well illustrated by the Programme's experience in 1989 and 1990. With a base year of 1988, when the US dollar was relatively low, TDR experienced a loss of about US\$ 1 100 000 on exchange rate changes in 1989, but a gain of about US\$ 644 000 in 1990, when the dollar again reached new lows.

FIGURE 6 Swiss Franc/US Dollar Average Annual Exchange Rates 1975-91



The negative effect of the decline in value of the US dollar is an increase in TDR costs, especially all Geneva-based expenditures and travel and meeting costs. The impact of currency fluctuations on the costs of TDR operations (research and development projects and research capability strengthening activities) is less immediate and difficult to assess, but there is undoubtedly an increase in project costs over time in countries whose currencies appreciate vis-à-vis the US dollar.

The impact of a declining US dollar is most apparent in the case of personnel costs. Personnel costs in the TDR Programme Budget for 1990-91 were based on standard WHO personnel costs, using a budget exchange rate of SFR 1.65 to the US dollar. The average rate of SFR 1.40 for 1990, combined with the continuing low rate likely for 1991, resulted in a major upward revision in the costs required for approved TDR posts in the biennium. The amount initially approved for Personnel Services in the 1990-91 Programme Budget was US\$ 11 955 200 (see Table 2.4) but it was necessary to increase this amount in the Revised Programme Budget for 1990-91 by an additional US\$ 1 627 100, to US\$ 13 582 300.

For 1992-93, standard personnel costs have been based on TDR's experience with actual expenditures for personnel in 1990 and an average exchange rate of about SFR 1.35 to the US dollar. Despite reductions in the number of staff paid by TDR - especially in WHO regional offices (see Sections 6 and 7), there is only a slight decrease in the financial requirements for staff costs (US\$ 52 300).

Another area with high price increases is international travel and per diems, which affects TDR operational support activities, such as the cost of STAC, RSG and Steering Committees etc. It is estimated that between late 1989 and late 1990, the average cost of travel and per diems for TDR-sponsored meetings increased by some 27%. Some of this cost increase has been absorbed by a reduction in the level of activity, for example by reducing the number of members of Steering Committees and in some cases the frequency of meetings. These measures result in a slight decrease in the budgeted amount for operational support.

2.2 Financing the Programme Budget

TDR depends on voluntary contributions from governments, international institutions, foundations and nongovernmental organizations for most of its income. Funds undisbursed at the end of each biennium become available in the subsequent biennium. Both the World Bank and WHO maintain undisbursed funds in interest-earning accounts that provide further sources of income.

Contributions required to finance the Proposed Budget for the 1992-93 Biennium are estimated at about US\$ 71.2 million. This represents an increase of US\$ 6.8 million over anticipated contributions of US\$ 64.4 million for the 1990-91 biennium. The carry-over of undisbursed funds from 1990-91 is projected to be US\$ 3.7 million. Interest and other income during 1992-93 is forecast to total US\$ 2.9 million. Total funds expected to be available to TDR during the 1992-93 biennium are estimated at US\$ 77.8 million. Based on obligations of US\$ 76.8 million projected in this Proposed Programme Budget, there is an estimated closing balance of US\$ 1.0 million at the end of the 1992-93 biennium (see Table 2.2).

TABLE 2.2 Estimated Financial Status 1992-93

<u>Source of Funds</u>	<u>US\$M</u>
Opening balance, 1 January 1992	3.7
Income:	
Contributions required	71.2
Interest	2.5
Other income *	0.4
Total Funds	77.8
<u>Application of Funds</u>	
Proposed Budget/Obligations	76.8
Closing balance, 31 December 1993	1.0
Total Applications	77.8

* Primary savings on unliquidated obligations.

2.3 Proposed Budget Allocations

TDR's budget may be classified in two dimensions: Programme Area/Component and Budget Element. The *Programme Areas (PA)* are:

- PA I *Technical and Administrative Bodies* includes the JCB, STAC, the Standing Committee and related items;
- PA II *Research and Development* covers budget provisions for the disease and trans-disease components;
- PA III *Research Capability Strengthening* includes the Epidemiology and Field Research Support Component; and
- PA IV *Programme Management* covers the Office of the Programme Director, programme management, information, communications, premises and other common services, as well as the costs of TDR-funded personnel in other WHO units.

Budget Elements, which provide a functional breakdown of the budget, are:

- Operations* - expenditures for research and development projects, institution strengthening activities and training activities;
- Personnel Services* - salaries and related costs for TDR staff, including temporary staff and staff in other WHO units;
- Operational Support* - meetings, consultants, temporary advisers and duty travel;

Technical and Administrative Bodies - corresponds to Programme Area I;

Other - expenditures for information services, public information and publications, office supplies, common services, premises and other items not included in other Budget Elements.

Tables 2.3 and 2.4 present proposed budget allocations by Programme Area and by Budget Element, with corresponding data for the budget initially approved by the JCB and the Revised Budget for the 1990-91 biennium. In terms of Programme Areas, the per cent allocated to Research Capability Strengthening (Programme Area III) will be 24.9%, slightly lower than in the Revised Budget for 1990-91. Research Capability Strengthening traditionally receives about 25 per cent of the total budget, in accordance with JCB decisions and recommendations of the first and second External Review Committees of TDR.

Within TDR Budget Elements, there will be an increase in the proportion of the budget devoted to Operations, from 71.5 per cent in the Revised Budget for 1990-91 to 73.1 per cent in 1992-93. Personnel Services will decline the most, from 18.6 per cent of the Revised Budget for 1990-91, to 17.6 per cent in 1992-93. Operational Support will decline by 0.4 per cent of the total budget, and there are also small decreases in Technical and Administrative Bodies and the "Other" Budget Element.

TABLE 2.3 Budget Summary by Programme Area (US\$000 and Per Cent)

PROGRAMME AREA	1990-1991		1992-1993	
	Approved Budget (1)	Revised Budget (2)	Proposed Budget (3)	Increase (Decrease) (3)-(2)
I Technical and Administrative Bodies	645.0	620.0	650.0	30.0
-- Per cent of Total	0.9	0.9	0.8	(0.1)
II Research and Development	46,043.5	45,901.0	49,655.0	3,754.0
-- Per cent of Total	63.1	62.9	64.6	1.7
III Research Capability Strengthening	18,905.2	18,270.0	19,150.0	880.0
-- Per cent of Total	25.9	25.1	24.9	(0.2)
IV Programme Management	7,346.5	8,132.3	7,390.0	(742.3)
-- Per cent of Total	10.1	11.2	9.6	(1.6)
TOTAL	72,940.2	72,923.3	76,845.0	3,921.7

TABLE 2.4 Budget Summary by Budget Element (US\$000 and Per Cent)

BUDGET ELEMENT	1990-1991		1992-1993	
	Approved Budget (1)	Revised Budget (2)	Proposed Budget (3)	Increase (Decrease) (3)-(2)
Operations	53,370.0	52,170.0	56,145.0	3,975.0
-- <i>Per cent of Total</i>	73.2	71.5	73.1	1.6
Personnel Services	11,955.2	13,582.3	13,530.0	(52.3)
-- <i>Per cent of Total</i>	16.4	18.6	17.6	(1.0)
Operational Support	4,700.0	4,316.0	4,200.0	(116.0)
-- <i>Per cent of Total</i>	6.4	5.9	5.5	(0.4)
Technical and Administrative Bodies	645.0	620.0	650.0	30.0
-- <i>Per cent of Total</i>	0.9	0.9	0.8	(0.1)
Other	2,270.0	2,235.0	2,320.0	85.0
-- <i>Per cent of Total</i>	3.1	3.1	3.0	(0.1)
TOTAL	72,940.2	72,923.3	76,845.0	3,921.7

3. PROGRAMME AREA I: TECHNICAL AND ADMINISTRATIVE BODIES

The budget allocation to this Programme Area covers the cost of meetings of the Joint Coordinating Board (JCB), the Standing Committee and the Scientific and Technical Advisory Committee (STAC). The amounts provide for one annual meeting each of the JCB and STAC and for three meetings of the Standing Committee per year. Provision is also made for scientific and technical reviews, including Prospective Thematic Reviews, carried out by STAC.

The biennial Programme Report is a formal report to the JCB and is an important source document for other interested individuals and institutions on the progress made by TDR-supported activities towards achieving the Programme's objectives. The provision covers the direct costs associated with the Programme Report, primarily editing, artwork, printing and translation.

Fundraising activities include visits to present and potential contributors for the purpose of increasing awareness of TDR and financial support for the Programme.

TABLE 3 Programme Area I: Technical and Administrative Bodies (US\$000)

Budget Item	1990-1991		1992-1993	
	Approved Budget (1)	Revised Budget (2)	Proposed Budget (3)	Increase (Decrease) (3)-(2)
Joint Coordinating Board (JCB)	140.0	140.0	140.0	0.0
Standing Committee	35.0	50.0	40.0	(10.0)
Scientific and Technical Advisory Committee	160.0	200.0	160.0	(40.0)
Scientific and Technical Reviews	100.0	60.0	100.0	40.0
Programme Report	160.0	120.0	150.0	30.0
Fundraising Activities	50.0	50.0	60.0	10.0
TOTAL	645.0	620.0	650.0	30.0

4. PROGRAMME AREA II: RESEARCH AND DEVELOPMENT

4.1 GENERAL ACTIVITIES

Budget provisions under General Activities cover research and development and operational support activities not assigned to a particular disease or trans-disease component or which involve several components.

The major budget item is the Director's Initiative Fund (DIF), which enables TDR to respond rapidly to innovative or promising research opportunities with limited amounts of "seed" funding. Support under the DIF is limited to US\$ 15 000 per project and is not renewable. If additional funds are required, requests are channelled to the relevant Steering Committee for consideration in the normal fashion. The DIF is also utilized to fund Project Development Grants, which provide assistance to researchers in developing countries to prepare proposals for submission to TDR Steering Committees.

In 1989 the Joint Coordinating Board approved an extension of the purpose of the Director's Initiative Fund, to permit the Director to increase the operations budgets of research and development components to meet new or increased financial requirements during the biennium. In 1990-91, an amount of US\$ 750 000 was reallocated from the DIF to three components: US\$ 300 000 to Schistosomiasis for vaccine development and multi-disease chemotherapy; US\$ 200 000 to Biological Control of Vectors for molecular entomology; and US\$ 250 000 to Social and Economic Research for drug distribution studies and other social and economic research projects.

The total amount proposed for the DIF in 1992-93 is US\$ 1 500 000, the same amount as the initially approved amount for 1990-91. About half of the amount is required for the small grants described above and the other half will be available for eventual reallocation to specific components during the biennium.

Operational support under General Activities covers meetings, temporary advisors, consultants and duty travel whose purpose cuts across several components or which cannot be assigned to a particular component. This provision is also used to supplement the operational support budgets of other research and development components as required during the biennium.

TABLE 4.1 General Activities (US\$000)

Budget Item	1990-1991		1992-1993	
	Approved Budget (1)	Revised Budget (2)	Proposed Budget (3)	Increase (Decrease) (3)-(2)
Director's Initiative Fund	1,500.0	750.0	1,500.0	750.0
Personnel Services	222.5	250.0	270.0	20.0
Temporary Assistance	100.0	160.0	150.0	(10.0)
Operational Support	750.0	400.0	500.0	100.0
Publications	250.0	275.0	250.0	(25.0)
Shipping and Insurance Adjustments	20.0	20.0	20.0	0.0
TOTAL	2,842.5	1,855.0	2,690.0	835.0

4.2 PRODUCT DEVELOPMENT

Objectives

- Assist in determining priorities for TDR product development
- Coordinate and support product development activities in TDR
- Provide development proposals and plans for specific product opportunities
- Undertake the development of certain priority products in close collaboration with the relevant components
- Manage integrated chemotherapy development for new chemoprophylactic agents against African trypanosomiases, Chagas disease and leishmaniases

Planned Activities 1992-93

The Joint Coordinating Board approved the establishment of the Product Development Unit at its Thirteenth Session in June 1990. Staffing began in August 1990 and preliminary activities got underway in 1991. The Product Development Unit is expected to be fully operational by January 1992. The Unit includes professional posts for biologicals and vaccines, chemotherapy, diagnostics and administration /data management. All posts are from existing resources (see Section 7 for details of the origin of the posts).

The work of the Product Development Unit will fall into three major areas:

- determining the TDR product portfolio
- providing proposals and plans for these product opportunities
- providing detailed management support and funding for selected products.

In consultation with the relevant staff of the Division of Control of Tropical Diseases (CTD) and the Secretaries of TDR Steering Committees, the product development needs required for TDR to meet its overall objectives for each disease category will be identified. Health care needs for disease control strategies will be major criteria for determining product development priorities. As far as possible, product specifications will be defined from potential user needs. The availability of existing products and those already in development and the technical, regulatory and ethical feasibility of development will also be important criteria.

Product development proposals and plans will be prepared in collaboration with the TDR Steering Committees and reviewed by a Product Development Committee comprising three external advisors experienced in product development, a representative of CTD, and the Head of PDU. Product development proposals will address user needs, the technical means of production, the demands and constraints of field testing and regulatory and ethical requirements. It will be important to provide realistic time lines for development activities, identify key checkpoints and estimate costs. Figure 6 summarizes the initial product development priorities identified in the Programme.

Product development activities will be financed generally by joint funding using the resources of the Product Development Component and of the relevant disease or trans-disease component. The Product Development Unit will have the responsibility to manage selected high priority products on a day to day basis, reporting progress to the relevant Steering Committee and to Director TDR.

Integrated chemotherapy development is directed towards a common strategic approach for drug development against three diseases, African trypanosomiases, Chagas disease and leishmaniases. Similarities among the causal parasites provide a rationale for drug development by virtue of common

therapeutic targets and chemical leads. A small scientific advisory group determines priority targets and compounds and develops concrete action plans for the development of these in collaboration with outside investigators and with industry.

FIGURE 7 Product Development Priorities

DISEASE	DRUGS	VACCINES AND BIOLOGICALS	DIAGNOSTICS
Malaria	Artemesinin and derivatives	Vaccines Anti-TNF antagonists	Dipstick tests to monitor serum anti-malarial drug levels
Schistosomiasis	Multi-disease chemotherapy	Recombinant vaccines	CAA diagnostic tests
Filariasis/ Onchocerciasis	CGP 6140 CGI 18041 UMF 078		Immunodiagnosics Vector diagnostics
African Trypanosomiasis	Eflornithine minimum dosage & combination therapy		Immunodiagnosics
Leishmaniases	Paromomycin ointment Amphotericin B formulation	Killed vaccines Recombinant vaccines	DAT-VL for sero-diagnosis of visceral leishmaniasis Antigen detection kit
Leprosy	Minocycline Ofloxacin Clarithromycin	Killed vaccines Recombinant vaccines	PCR diagnostics
Chagas Disease	Allopurinol		Blood bank diagnostic
Biological Control of Vectors		<i>B. sphaericus</i>	

TABLE 4.2 Product Development (US\$000)

Budget Item	1990-1991		1992-1993	
	Approved Budget (1)	Revised Budget (2)	Proposed Budget (3)	Increase (Decrease) (3)-(2)
Operations:-				
Product Development	-	-	4,500.0	4,500.0
Integrated Chemotherapy Development	-	-	1,000.0	1,000.0
Personnel Services	-	-	1,270.0	1,270.0
Operational Support	-	-	200.0	200.0
TOTAL	-	-	6,970.0	6,970.0

4.3 CHEMOTHERAPY OF MALARIA

Objectives

- Develop new drugs for the treatment and prevention of malaria
- Improve the use of drugs which are already available
- Promote basic research aimed at identifying new approaches to malaria chemotherapy

Planned Activities 1992-93

Clinical trials of several dosage forms of artemisinin (Qinghaosu) and its derivatives will dominate product development activities in 1992-93. Preclinical and phase I clinical trials completed in 1991 for artemether and arteether intramuscular dosage forms will form the basis of expanded phase II and phase III clinical trials in endemic countries, with emphasis on evaluation of safety and efficacy in the treatment of severe and complicated malarias. Concurrently, consultations with Chinese manufacturers will strengthen good manufacturing practices and quality assurance. Manufacturing development for an arteether injection and potentially other parenteral and oral dosage forms will be supported, and non-clinical and clinical data bases will be developed to support registration of selected products in developed and developing countries. The synthesis of novel derivatives will also be continued. The development of artemisinin and certain derivatives will be carried out with the collaboration of ACF Beheer, B.V., for which special project funding is included in the Revised Budget for 1990-91 (US\$ 400 000) and the Proposed Budget for 1992-93 (US\$ 1.0 million).

The emergence of parasite resistance to mefloquine and quinine, particularly in South-East Asia, requires urgent and decisive research to identify alternative therapeutic strategies to include, but not limited to, the introduction of artemisinin products. Alternative regimes of mefloquine, mefloquine combinations, and halofantrine will be explored clinically. Improved strategies for use of quinine in severe and complicated malaria will also be investigated.

Several candidate drugs have emerged which reverse chloroquine resistance, and in some cases mefloquine resistance. Although all known candidates are limited by kinetics and by a narrow margin between effectiveness and toxicity, preclinical and phase I clinical studies are continuing with one candidate reverser, which will be evaluated in malaria patients if initial studies give promising results.

Initial Phase I and Phase II studies of a new hydroxynaphthoquinone (BW 566) will be completed in 1991 by the Wellcome Foundation. TDR will support expanded trials of this compound in developing countries to define operational utility and support registration. TDR will also participate in clinical evaluation of an intravenous dosage form of halofantrine which has been developed outside the Programme, as well as the evaluation of halofantrine in chemoprophylaxis.

To the extent possible within constrained financial resources, TDR will continue to support research on parasite biology and biochemistry with the objective of identifying targets for design of novel chemotherapeutic agents and strategies. Research directed towards improved use of older drugs will focus on combination therapies, improved dosage forms, and definition of relevant adverse reactions.

TABLE 4.3 Chemotherapy of Malaria (US\$000)

Budget Item	1990-1991		1992-1993	
	Approved Budget (1)	Revised Budget (2)	Proposed Budget (3)	Increase (Decrease) (3)-(2)
Operations	5,200.0	5,400.0	5,600.0	200.0
Personnel Services	500.5	600.0	400.0	(200.0)
Operational Support	325.0	290.0	300.0	10.0
TOTAL	6,025.5	6,290.0	6,300.0	10.0

4.4 IMMUNOLOGY OF MALARIA

Objectives

- ° Develop malaria vaccines
- ° Improve diagnostic tests for malaria
- ° Explore biologicals for treatment of malaria

Planned Activities 1992-93

Vaccines based on antigens of asexual blood-stages of plasmodia are expected to reduce morbidity and mortality due to malaria. Over half of the component budget is devoted to analysis of the antigenic components of asexual blood-stages of *Plasmodium falciparum* and the immune responses they evoke. Major priority will continue to be given to this area in 1992-93. From the many *P. falciparum* antigens identified, a short list of promising vaccine candidates is emerging, some of which may be used in combination. Initial clinical testing is expected during the biennium.

Vaccines based on antigens of the sexual and sporogonic stages, which develop in the mosquito vector, will help to protect vaccinated communities by reducing the level of malaria transmission. If used in combination with a protective sporozoite and/or asexual stage vaccine, such vaccines should prevent the propagation of vaccine-resistant mutant parasites. TDR has supported all of the laboratories working in this area and has prepared a strategy to promote vaccine development in collaboration with industry. Exploration of different expression systems for the production of recombinant Pfs25 will be supported and initial clinical trials may take place during the biennium. Support will continue for completion of gene cloning and expression of other potential vaccine target molecules of both *P. falciparum* and *P. vivax*.

The development of pre-erythrocytic vaccines will continue to be a priority. Vaccines based on antigens of sporozoites and liver stages should prevent the establishment of infection in the vaccinated subject. Following the cloning of the genes encoding the circumsporozoite proteins of *P. falciparum* and *P. vivax*, supported in part by TDR, several recombinant and synthetic vaccine constructs were tested in human subjects with some encouraging results. TDR will continue to fund research on the elucidation of the immunological mechanisms involved in pre-erythrocytic immunity, an essential prerequisite for the design of more effective vaccines.

TDR will continue to support the development of ELISA-based test kits for the detection and identification of sporozoites in mosquitoes, using a monoclonal antibody to the circumsporozoite protein (CSP). Kits for the identification of *P. falciparum* and *P. vivax* will be used in field studies and in malaria control activities. Following the identification of *P. vivax* sporozoites bearing a variant of the CSP, a second version of the *P. vivax* kit will be developed. Test kits for *P. ovale* sporozoites will also be produced during the biennium.

Evidence for the implication of tumor necrosis factor (TNF) in the pathogenesis of cerebral malaria provided the rationale for a recent TDR-supported pilot clinical trial of an anti-TNF monoclonal antibody in children with cerebral malaria. The results of the trial will provide a basis for planning further investigations on the potential value of modifying TNF levels in severe malaria.

TDR will continue to support basic research on malaria parasites, including analysis of the structure and function of malaria antigens and the immune responses they induce. Vaccine development will continue to require the support of a basic research programme in relation to rational vaccine design and the evaluation of candidate vaccines.

TABLE 4.4 Immunology of Malaria (US\$000)

Budget Item	1990-1991		1992-1993	
	Approved Budget (1)	Revised Budget (2)	Proposed Budget (3)	Increase (Decrease) (3)-(2)
Operations	5,000.0	4,700.0	4,400.0	(300.0)
Personnel Services	300.0	360.0	400.0	40.0
Operational Support	275.0	275.0	250.0	(25.0)
TOTAL	5,575.0	5,335.0	5,050.0	(285.0)

4.5 APPLIED FIELD RESEARCH IN MALARIA

Objectives

- Investigate the epidemiology of malaria to develop control strategies to reduce morbidity and mortality
- Improve malaria control through research on innovative control measures
- Develop, validate and field test malaria control methods and transfer the resulting techniques to appropriate areas

Planned Activities 1992-93

Malaria incidence and prevalence appears to be on the increase in many parts of the world. Malaria is a major cause of mortality, particularly among children in highly endemic areas of tropical Africa. Chloroquine resistance has spread to most African and Middle East countries where *Plasmodium falciparum* is endemic. Sensitivity to sulphadoxine plus pyrimethamine remains satisfactory in most of Africa, but sensitivity to these plus other new compounds is diminishing in other areas, particularly South-East Asia.

In the face of these demoralizing facts, research supported by TDR suggests that chemoprophylaxis in African children can reduce mortality and morbidity and does not seem to impair immunity. New cytogenetic, enzymatic and immunological tools have shown epidemiologically important genetic heterogeneity in parasites and vectors and have allowed the vectorial role to be clarified for several situations. Among potential control methods, insecticide impregnated bednets seem especially promising, reducing mortality by approximately 60% in children one to four years old in one study in Africa.

Immunological studies have shown that naturally acquired immunity to sporozoites requires long and repeated exposure. Several asexual blood stages of parasites have revealed antigenic diversity potentially important for the selection of vaccine candidates.

Trends in research applications have shown a marked increase in the quality, quantity and cost of projects in applied field research in malaria. For example, the evaluation of the potential of insecticide treated bednets from an operational standpoint has attracted a number of researchers in several African countries.

Further emphasis will be placed in four main areas:

- Identification of risk factors for severe and complicated malaria and possible strategies for reducing morbidity and mortality from severe disease will be of highest priority.
- The development and evaluation of malaria control strategies with particular attention to operational problems will be a major priority, in collaboration with the WHO Malaria Unit. This will include the use of insecticide impregnated bednets, alternative drugs, prevention of malaria in pregnancy and the development and testing of new diagnostic methods. The development and validation of the paradigm approach to malaria control will be carried out in conjunction with the Malaria Unit.
- Determination of epidemiological factors relevant for the development of malaria vaccines through studies on the patterns of inoculation and the development of acquired immunity, antigenic diversity and the protection associated with immune response to candidate antigens for vaccines will continue to be explored.
- Improvement of vector control through a better knowledge of the behaviour and vectorial role of several anopheles species in specific ecotopes, and the adaptation of established vector control tools will also remain a focus.

TABLE 4.5 Applied Field Research in Malaria (US\$000)

Budget Item	1990-1991		1992-1993	
	Approved Budget (1)	Revised Budget (2)	Proposed Budget (3)	Increase (Decrease) (3)-(2)
Operation	3,000.0	3,500.0	3,300.0	(200.0)
Personnel Services	300.0	325.0	400.0	75.0
Operational Support	200.0	250.0	250.0	0.0
TOTAL	3,500.0	4,075.0	3,950.0	(125.0)

4.6 SCHISTOSOMIASIS

Objectives

- ° Develop a vaccine capable of providing long-term protection against morbidity
- ° Develop new and improved approaches for control of morbidity and transmission of schistosomiasis
- ° Develop simple field diagnostic methods
- ° Develop safe and reliable drugs, and drug combinations for multidisease chemotherapy

Planned Activities 1992-93

A vaccine would provide an immensely useful long term contribution to control, particularly if combined with the use of praziquantel, against which drug resistance has not yet developed. For this reason, there is a strong emphasis on vaccine development along three lines: against parasite infection and development aiming at reducing the number of adult worms in the human host; an anti-fecundity approach directed at reducing the number of eggs produced by each worm pair; and an anti-pathological line directed at reducing the granulomatous reaction to eggs deposited in the tissues of the host. Rather than completely blocking infection, a combination of these approaches aims at controlling morbidity.

A number of on-going projects address the question of immunological mechanisms and human acquired immunity. Since none of the approximately 30 available cloned schistosome antigens consistently induce useful protection, testing of antigen combinations has been initiated. This initiative is expected to increase the number of immunological projects in the future.

Active intervention at the preproposal phase resulted in funding of 14 new field research projects in 1989-90. This research involves different combinations of tools such as chemotherapy, snail control, water supply, sanitation and health education. Application of ultrasound for assessment of morbidity in the field has proved to be increasingly useful and the implementation of standardized guidelines are currently being followed up. Phase II and III trials using combinations of praziquantel and a

benzimidazole to treat simultaneously schistosomiasis and intestinal parasites are envisaged, with the ultimate aim of reducing costs of drug distribution. This research is undertaken in close collaboration with the Division of Communicable Diseases (CDS), which is responsible for intestinal parasites.

There is a clear need for improved diagnostic tools for diagnosis of schistosomiasis, particularly in well controlled areas. Continuing support of trials is envisaged using field - and laboratory-based methods to compare diagnostic approaches focussed on specific antibodies, circulating antigens or antigens or DNA excreted in the urine. This research is also relevant for vaccine development since correct assessment of worm burden will be important in the evaluation of future vaccine trials.

Research on new drugs includes attempts at inhibition of a schistosome neuropeptide and interference with the hormones regulating egg-laying. In addition, the synergism between drugs and antibodies is being studied as well as the mode of action of currently used drugs. Toxicity studies of molluscicides are supported with the aim of finding affordable locally available means of snail control.

TABLE 4.6 Schistosomiasis (US\$000)

Budget Item	1990-1991		1992-1993	
	Approved Budget (1)	Revised Budget (2)	Proposed Budget (3)	Increase (Decrease) (3)-(2)
Operations	2,500.0	2,700.0	2,050.0	(650.0)
Personnel Services	300.0	420.0	400.0	(20.0)
Operational Support	200.0	170.0	200.0	30.0
TOTAL	3,000.0	3,290.0	2,650.0	(640.0)

4.7 FILARIASIS

Objectives

- Obtain and develop better drugs and drug regimens for treatment of lymphatic filariasis and onchocerciasis
- Develop better diagnostic tests
- Reduce inflammatory reaction in patients with clinical disease
- Improve the scope and efficacy of methods of filarial disease prevention

Planned Activities 1992-93

The search for new filaricides, especially macrofilaricides, for both lymphatic filariasis and onchocerciasis will continue as a high priority. This search for a single-dose, non-toxic macrofilaricide will be carried out through biochemical studies, screening and synthesis. Two new compounds which have potential, University of Michigan UMF-078 and Ciba Geigy CGP-18041, will be further developed

and may lead to phase I clinical trials in 1992-93. Research and development for macrofilaricides is carried out in close cooperation with the Onchocerciasis Control Programme in West Africa (OCP), under a joint OCP/TDR macrofilaricide project.

The use of ivermectin as a safe, tolerable and efficacious drug for onchocerciasis has been established through earlier clinical trials. The drug will continue to be tested in the field to assess its impact on transmission of onchocerciasis, especially in Latin America.

Studies with ivermectin in lymphatic filariasis have shown in the past two years that it is an excellent drug to reduce microfilariae in a single oral dose. Clinical studies to compare the efficacy of ivermectin to diethylcarbamazine (DEC) using various dose regimens will be carried out in Brazil, Kenya, Haiti, India, Papua New Guinea, and Tahiti. Clinical trials of ivermectin in combination with DEC are also planned to assess macrofilaricidal action, in addition to evaluating the effect of ivermectin in clinical disease in lymphatic filariasis.

For both onchocerciasis and lymphatic filariasis, research will continue for sensitive and specific diagnostic tests for prepatent, patent and occult infection. A multicentre study with antigens selected from a large pool of recombinant antigens has already been planned using well characterized serum from endemic countries. DNA probes for diagnosis of infection in lymphatic filariasis to replace cumbersome night blood examination are also planned. Some of the more promising tests will lead to the development of field test kits.

Similarly, development of DNA probes to detect and differentiate infected larvae of *Onchocerca volvulus*, *Wuchereria bancrofti* and *Brugia malayi* in vector species have made considerable advance and it is anticipated that these probes will be field tested in control programmes to monitor transmission. Plans are also being prepared to produce easily usable DNA probe field kits for detection of infection in vectors. The technology for distinguishing savannah from forest forms of onchocerciasis will be transferred to a West African country.

In collaboration with the Biological Control of Vectors Component, large-scale trials to control *Culex quinquefasciatus* using *Bacillus sphaericus* are planned in selected areas in Brazil, India and Tanzania and will be initiated during 1992-93.

TABLE 4.7 Filariasis (US\$000)

Budget Item	1990-1991		1992-1993	
	Approved Budget (1)	Revised Budget (2)	Proposed Budget (3)	Increase (Decrease) (3)-(2)
Operations:-	4,200.0	3,750.0		(250.0)
Filariasis General			2,600.0	
OCP/TDR Macrofil			900.0	
Personnel Services	300.0	390.0	400.0	10.0
Operational Support	275.0	335.0	300.0	(35.0)
TOTAL	4,775.0	4,475.0	4,200.0	(275.0)

4.8 AFRICAN TRYPANOSOMIASES

Objectives

- Strengthen disease control through a better understanding of the epidemiology and use of vector control methods
- Develop new and effective drugs and drug combinations and improve the use of existing drugs
- Improve patient management through better knowledge of the disease's immunology and pathology

Planned Activities 1992-93

Following successful experimental use of eflornithine to treat over 600 *gambiense* sleeping sickness patients, the drug was registered in the United States in November 1990. Research will continue on the minimum effective dose, in order to reduce the duration and cost of treatment. Clinical trials are also in progress with eflornithine combined with suramin as therapy for *rhodesiense* sleeping sickness.

Transfer to a developing country of the production technology of eflornithine has been given an impetus by the offer of Marion Merrell Dow to WHO, of the patent and technical know-how for the manufacture of eflornithine on a royalty free basis. The identification of a suitable developing country location for manufacturer of eflornithine is therefore a priority.

The search for lead compounds for drug development will continue by screening of compounds supplied by industry. Biochemical targets include glycolytic enzymes, nine of which have been crystallized, and trypanothione biosynthesis and function.

Studies on the role and significance of animal reservoirs in the epidemiology of African trypanosomiasis are a high priority. In the current *rhodesiense* sleeping sickness epidemic in Busoga in Uganda, 25 per cent of *Trypanosoma brucei* infection isolated from cattle were similar biochemically to trypanosomes infective to man, indicating that cattle are important reservoir of infection. The systematic treatment of cattle is being undertaken as an integral part of sleeping sickness control strategy in these areas.

Research continues on traps and screens to control tsetse flies. Ten thousand pyramidal traps deployed during the past two years to control tsetse in the Busoga area have contributed to substantive decrease in incidence of sleeping sickness. In peripheral areas where no traps are being used, active transmission has been taking place and traps will be introduced in the near future. Further research to improve traps and operational research on social acceptability and community participation in the use of traps will continue.

Results of the evaluation of the Antigen Detection Enzyme Immunoassay for the detection of active infection were satisfactory regarding the sensitivity and specificity. Evaluation will continue and revision of the assay is envisaged as the current presentation is cumbersome. The Polymerase Chain Reaction (PCR) will be explored for detection of parasites in cerebrospinal fluid.

The Procytic Agglutination Test for Trypanosomiasis (PATT) has been adapted for field use and will be evaluated in Côte d'Ivoire.

Another important area of research is on the pathogenesis of the disease, which is useful for devising approaches to patient management. Studies in experimental models have shown that the early invasion of areas lacking blood brain barrier or blood nerve barrier may relate to cardinal symptoms of the disease, and that late stage manifestations of the disease may result from widespread imbalances in the levels of cytokines such as PGD₂, throughout the neuraxis, caused by parasite/astrocyte/lymphocyte and other blood component interactions rather than any specific localized lesion in particular brain areas.

TABLE 4.8 African Trypanosomiases (US\$000)

Budget Item	1990-1991		1992-1993	
	Approved Budget (1)	Revised Budget (2)	Proposed Budget (3)	Increase (Decrease) (3)-(2)
Operations	2,800.0	2,700.0	2,000.0	(700.0)
Personnel Services	300.0	430.0	340.0	(90.0)
Operational Support	200.0	200.0	200.0	0.0
TOTAL	3,300.0	3,330.0	2,540.0	(790.0)

4.9 CHAGAS DISEASE

Objectives

- ° Large-scale evaluation of new vector control methods in different entomological and epidemiological situations
- ° Develop kits for blood screening using synthetic and/or recombinant defined antigens
- ° Evaluate the effect of drugs in the chronic phase of the disease
- ° Improve knowledge of parasite molecular biology and pathogenesis of the disease to promote vaccine development

Planned Activities 1992-93

The efficacy, acceptability and cost-effectiveness of insecticidal paints and fumigant canisters developed with TDR support will be tested under standard protocols in five Latin American countries: Argentina, Bolivia, Chile, Honduras and Paraguay. A revised strategy for vector control in each endemic country will be worked out in close collaboration with the Pan American Health Organization (PAHO), bilateral agencies and the Inter-American Development Bank (IDB). By doing so, it is expected to contribute to the aims of a resolution on elimination of vectorial transmission of Chagas disease approved by the 23rd Pan American Sanitary Conference in September 1990.

High priority will be assigned to the development of kits for blood screening in blood banks in collaboration with manufacturers in endemic countries, using recombinant and/or synthetic defined antigens. This activity should complement the vector control strategies since it is aimed at the interruption of transmission of the infection via blood transfusion in urban areas. The defined molecules will be those that showed highest sensitivity and specificity in a multicentre blind study involving ten laboratories in Latin America carried out in 1990.

A multicentre clinical trial will be completed in Cordoba (Argentina), Santacruz (Bolivia) and Goias (Brazil) to assess the parasiticide activity of allopurinol in the chronic phase of the disease. Basic research on molecular biology, molecular genetics and immunology will continue to understand better the mechanisms involved in the genesis of chronic lesions in order to develop a safe and protective vaccine.

TABLE 4.9 Chagas Disease (US\$000)

Budget Item	1990-1991		1992-1993	
	Approved Budget (1)	Revised Budget (2)	Proposed Budget (3)	Increase (Decrease) (3)-(2)
Operations	2,100.0	2,150.0	1,825.0	(325.0)
Personnel Services	300.0	340.0	340.0	0.0
Operational Support	200.0	200.0	200.0	0.0
TOTAL	2,600.0	2,690.0	2,365.0	(325.0)

4.10 LEISHMANIASES

Objectives

- ° Develop vaccines against cutaneous forms of the disease
- ° Develop a non-invasive test for visceral leishmaniasis
- ° Develop a topical treatment for cutaneous leishmaniasis
- ° Use available drugs more efficiently
- ° Develop tools for the control of reservoir hosts and vectors

Planned Activities 1992-93

During the 1990-91 biennium, planned phase I and II trials of the killed *Leishmania major* + BCG vaccine against cutaneous leishmaniasis should be completed. Based on the findings, additional dose-finding and safety studies in adults and phase III studies (efficacy in the field) can be initiated. Depending upon the progress of the phase I trial of a killed *Leishmania* + BCG vaccine in Brazil, phase II or III trials are envisaged against New World cutaneous leishmaniasis in Brazil. Baseline epidemiological information will be required before and during the evaluation studies of these vaccines.

Candidate second generation vaccines against cutaneous and visceral leishmaniasis will be tested in animal models. Baseline information on infection, challenge system and key immune parameters will continue to be obtained and a reproducible system will hopefully be developed before testing the candidate vaccines. The search for immunological indicators responsible for or correlating with protection in humans and animal models will continue through different phases.

The Direct Agglutination Test (DAT) for diagnosis of visceral leishmaniasis will be standardized and field tested with the view to eliminating the need for obtaining spleen or bone marrow biopsies.

An ointment containing the antibiotic paromomycin will be tested against cutaneous leishmaniasis to replace the need for systemic treatment with antimonials.

The search for parasite components in body fluids will hopefully reveal the presence of key parasite components which could be used for evaluation of therapy and the determination of time for cessation of treatment (test for cure). These studies have just started. The Polymerase Chain Reaction (PCR) has been adapted to field conditions and will continue to be simplified and used for diagnosis, test for cure and prognosis - particularly for mucocutaneous leishmaniasis. The selection of key monoclonal antibodies and/or antigens for identification of parasite and for use in diagnostics will be accomplished.

Studies on immunotherapy against different forms of leishmaniasis will continue and cytokine production in response to different antigens will be pursued during the recovery phase. These studies will likely continue as new cytokines are discovered and new methodologies are developed.

Following the initial trials (outside TDR) of amphotericin B preparations in new carriers (lipid complex, liposomes), clinical and field trials will be conducted against various forms, particularly visceral and mucocutaneous leishmaniasis.

Initiation of pilot control studies based on vector and reservoir control has been delayed and is likely to begin in 1991. The use of insecticide impregnated curtains, diagnosis and treatment of cases and detection and elimination of infected dogs in well studied foci will continue for testing new tools and for training.

Fundamental studies in immunology, parasite biochemistry and genetics, and vector biology will be supported to the extent possible.

TABLE 4.10 Leishmaniases (US\$000)

Budget Item	1990-1991		1992-1993	
	Approved Budget (1)	Revised Budget (2)	Proposed Budget (3)	Increase (Decrease) (3)-(2)
Operations	2,500.0	2,500.0	2,350.0	(150.0)
Personnel Services	300.0	420.0	400.0	(20.0)
Operational Support	200.0	266.0	200.0	(66.0)
TOTAL	3,000.0	3,186.0	2,950.0	(236.0)

4.11 LEPROSY

Objectives

- ° Promote research leading to improvement in the use of existing drugs and regimens
- ° Develop new drugs, new combinations of drugs and new approaches for monitoring chemotherapy
- ° Develop vaccines and effective ways of using them
- ° Develop new tools for laboratory and field use in epidemiological studies
- ° Improve understanding of the immunopathology of the disease in order to control and prevent the reactions and nerve damage which lead to deformities

Planned Activities 1992-93

Two large-scale long-term leprosy vaccine trials involving a total of approximately 155 000 study subjects are currently underway in Malawi and Venezuela, with preliminary results expected from the Venezuelan trial in late 1991. A third major multi-arm vaccine trial will be initiated in early 1991, in South India near Madras, organized and supported by the Indian Council of Medical Research (ICMR). This important vaccine trial will allow the comparison of several cultivable vaccine candidates already under development in India with the armadillo-derived, heat-killed *Mycobacteria leprae* vaccine provided by TDR. Initial results for this trial will be available around the year 2000.

The identification, characterization and development of second generation vaccine candidates, including the development of appropriate vaccine vehicles such as BCG, salmonella and vaccinia will be continued. Considerable progress has been made in the construction of recombinant BCG strains, based on recent advances in the field of mycobacterial molecular genetics. In order to evaluate the potential protective efficacy of these new vaccine candidates, appropriate animal models such as the immunodeficient SCID mice or non-human primates will be developed.

The identification and development of new immunodiagnostic tests for epidemiological use, include the detection of *M. leprae* infection, will be promoted, based on synthetic peptides, recombinant proteins and DNA/RNA probe-based assays such as the Polymerase Chain Reaction (PCR). These tools are required for monitoring of *M. leprae* infection patterns in the community subsequent to interventions such as multi-drug therapy and vaccination, as a surrogate measure for disease transmission.

The study of the various reactional states of leprosy which often lead to nerve damage represents another area of research for 1992-93, since a better understanding of molecular mechanisms of reactions and nerve damage has a direct relevance to developing novel strategies for diagnosis, prevention of the development of disabilities and successful treatment of leprosy patients.

With respect to chemotherapy, the currently recommended WHO multidrug therapy (MDT) for the treatment of multi- and paucibacillary leprosy is being evaluated in terms of occurrence of relapse following completion of treatment, occurrence of late reversal reactions, and impact of MDT on transmission of disease/infection. In addition, fixed duration MDT, limiting treatment of multibacillary leprosy to two years, will continue to be evaluated. Studies of one year fixed duration MDT will also be initiated. Special studies to monitor the occurrence of drug resistance to multiple drugs will be promoted in areas where MDT is possibly applied in an irregular manner.

Emphasis in the development of new drugs for treatment of leprosy will continue to be on screening drugs known to have anti-mycobacterial activity. Such drugs will be screened in the mouse footpad system and if found effective, short term clinical trials will be initiated after other requirements for use in leprosy patients have been met. In this area a number of fluoroquinolones and possibly some other compounds are expected to be screened. The current short term clinical trials of ofloxacin, minocycline and clarithromycin will be continued and extended to identify the best possible regimens for these drugs.

A major activity in 1992-93 and beyond will be field trials with multidrug regimens containing ofloxacin. While this activity will involve a multicentre approach employing standard protocols, it will not exclude other possibilities of studying ofloxacin in the treatment of leprosy. Minocycline and clarithromycin are likely to reach the stage of field trials, and optimal ways of employing them will be identified. With evidence becoming available that 1 200 mg of clofazimine once a month is as effective as 50 mg daily together with 300 mg once a month as administered under the current WHO/MDT regimen, new MDT regimens, dependent mainly upon once a month administration of drugs, will be developed.

Development of tools including DNA probes to identify viable *M. leprae* that would enable rapid drug screening and screening for drug resistance will be supported. Studies on mechanisms of reactions and nerve damage will be continued. Operational research in leprosy control will also be pursued.

TABLE 4.11 Leprosy (US\$000)

Budget Item	1990-1991		1992-1993	
	Approved Budget (1)	Revised Budget (2)	Proposed Budget (3)	Increase (Decrease) (3)-(2)
Operations:-				
Immunology	3,300.0	3,100.0	2,500.0	(600.0)
Chemotherapy	2,300.0	1,800.0	1,400.0	(400.0)
Personnel Services	600.0	460.0	400.0	(60.0)
Operational Support	400.0	600.0	300.0	(300.0)
TOTAL	6,600.0	5,960.0	4,600.0	(1,360.0)

4.12 BIOLOGICAL CONTROL OF VECTORS

Objectives

- ° Identify and develop natural biological regulators of vector populations
- ° Improve the properties of existing biocontrol agents
- ° Introduce innovative approaches for vector control by modern biotechnology methods

Planned Activities 1992-93

Several biological agents with vector control potential are now used in disease control programmes. *Bacillus thuringiensis* H-14 is efficiently applied against blackfly vectors of onchocerciasis in West Africa, against mosquito vectors in China, USSR and against nuisance mosquitos in the USA, Canada and some European countries. *B. sphaericus* has shown good results for the control of *Culex* and some *Anopheles* and *Mansonia* mosquito species. Operational research and large-scale trials of these microbials and epidemiological evaluation of their efficacy in lymphatic filariasis and malaria endemic areas will now receive high priority.

Ecological studies of freshwater habitats provide basic data for understanding the recycling potential of biological agents and larval food sources. A number of new agents pathogenic for vectors have been discovered by the network of collaborative laboratories and now some will be tested for safety and further developed (e.g. *Clostridium bifermentans*, *B. brevis*, new strains of *B. sphaericus* and *B. thuringiensis*, *Aspergillus* fungi). The search for new pathogens, especially those indigenous to tropical environments, be continued by several laboratories.

Studies on toxin production, genetic coding and mode of toxin action confirmed the possibility of producing more potent larvicidal bacterial agents by means of genetic engineering. Genetically modified organisms showed a good potential for vector control in laboratory studies; their stability, safety and possible environmental impact will be evaluated for further development.

A major new challenge for the future will be the development of innovative strategies for malaria control by genetic manipulation of its vectors. Recent biotechnological advances in the area of vector-parasite relationship support the possibility of genetic modifications of *Anopheles* vectors in order to disrupt the parasite cycle. The steps necessary to achieve this goal would involve the solution of various laboratory and field problems such as an understanding of the molecular basis of vectorial competence, the development of molecular tools for engineering a refractory mosquito and the understanding of mosquitos population dynamics to effectually apply this new methods into the field. New tools for malaria control might emerge through this type of research.

TABLE 4.12 Biological Control of Vectors (US\$000)

Budget Item	1990-1991		1992-1993	
	Approved Budget (1)	Revised Budget (2)	Proposed Budget (3)	Increase (Decrease) (3)-(2)
Operations	1,800.0	1,900.0	1,750.0	(150.0)
Personnel Services	300.0	350.0	400.0	50.0
Operational Support	200.0	150.0	200.0	50.0
TOTAL	2,300.0	2,400.0	2,350.0	(50.0)

4.13 SOCIAL AND ECONOMIC RESEARCH

Objectives

- ° Increase the effectiveness of disease control activities by integrating social and economic factors into the design and management of control strategies
- ° Promote the development and application of cost-effective, acceptable disease control measures and policies
- ° Promote the development and application of rapid assessment and other advanced social science methods to tropical disease control

Planned Activities 1992-93

In 1992-93 TDR will expand its support for research on the economic aspects of tropical diseases. The cost-effectiveness and social acceptability of tools for the control of the TDR target diseases will be given priority. Studies to evaluate Chagas disease control measures have already been supported in several countries and it is expected that similar evaluation components will be built into field trials of other TDR supported products including, for example, impregnated bednets and vaccines against leprosy. Costing studies will continue to be funded on a selective basis, particularly with respect to the cost of delivering ivermectin and anti-schistosomal drugs. Health services research, focusing on the costs and effectiveness of alternative delivery and health education strategies, alternative distribution mechanisms and the impact of incentives for health workers on performance, will also be encouraged. A selected number of studies on the impact of cost recovery and user charges schemes on TDR's target diseases are likely to be supported.

TDR will continue to assist research on ivermectin delivery in West Africa. In Nigeria support for operational research accompanying the introduction of ivermectin is currently being provided through a programme of small grants, administered jointly by the Nigerian Onchocerciasis Control Programme and TDR. In Latin America TDR will continue to provide support for research on social and economic factors involved in the control of onchocerciasis through ivermectin.

Techniques for stimulating greater community involvement in disease control will be developed and tested, including the relative effectiveness of involving groups such as teachers and students and different communications strategies for health education. A multi-country study on community perceptions of urinary schistosomiasis, completed in 1991, will likely be followed by a study involving schools and key community members in drug distribution in conjunction with community health care services.

Since 1990, several studies have been funded on risk factors for women with respect to the tropical diseases, as well as selected intervention studies. Policy recommendations to support special programmes for women for tropical disease prevention and control, as well as for their increased involvement in these activities, will likely be made to the World Health Assembly, based on the findings of research currently underway.

Another focus will be the development and application of rapid assessment methods to TDR's target diseases for a number of important purposes, such as the identification of high risk areas or communities suitable for the introduction of field trials. TDR will also investigate the utility of more advanced methodological approaches to the study of tropical diseases. The use of modelling, for example, to examine the implications of alternative control strategies, already underway with respect to helminth infections and leprosy, for other TDR target diseases will also be explored.

TABLE 4.13 Social and Economic Research (US\$000)

Budget Item	1990-1991		1992-1993	
	Approved Budget (1)	Revised Budget (2)	Proposed Budget (3)	Increase (Decrease) (3)-(2)
Operations	1,650.0	2,100.0	2,000.0	(100.0)
Personnel Services	500.5	600.0	740.0	140.0
Operational Support	375.0	315.0	300.0	(15.0)
TOTAL	2,525.5	3,015.0	3,040.0	25.0

5. PROGRAMME AREA III: RESEARCH CAPABILITY STRENGTHENING

Objective

- To strengthen, through research training and institutional support, research capabilities in disease endemic countries, enabling these countries to undertake research relevant to the control of tropical diseases and to participate in the global effort to develop new methods of prevention, diagnosis and treatment of TDR target diseases

Planned Activities 1992-93

Institution Strengthening

Twenty-eight institutions were funded in 1990 utilizing the new mechanisms established during the 1988-89 biennium. An in-depth review of the TDR-Rockefeller Foundation Joint Programme and of programme-based grants is scheduled in 1991 and 1992 respectively. It is anticipated that institutions involved in these grants will become major focal points for training researchers from disease endemic countries.

Institution strengthening efforts during 1992-93 will be directed especially to least developed countries where TDR activities have been minimal so far. As formal institutions devoted to research in parasitic diseases may not be present in most of these countries, strengthening research capability may be initiated through training and through flexible mechanisms in close collaboration with other WHO efforts and bilateral and international support programmes. These efforts will concentrate on building up their essential national health research capability.

Several least developed countries will be selected each year for concentrated efforts and specific strategies for institution strengthening developed after on-the-spot assessments. Research training will be accompanied by re-entry grants which will permit initiation by trainees of suitable time limited research/study projects in their home countries on priority subjects. Links will be promoted between scientists and other institutions in the region strengthened by TDR through the FIELDLINCS mechanism (see Section 5.1).

Countries where several institutions have already been strengthened will be encouraged to apply to the various TDR Scientific Steering Committees for support of specific research and development projects.

During 1992-93 conventional institution strengthening grants will gradually be phased down. Opportunity will be provided to research institutions and groups (including those who have previously received TDR grants) to apply for another round of programme-based grants. This will provide further impetus to building human and institutional resources in developing countries to fulfill TDR's research and development objectives, as well as encouraging strong linkages between researchers and disease control programmes.

In order to build up capacities for research in social sciences in developing countries, a number of programme grants will be funded in the social sciences. These will provide for the establishment of senior social science posts, research fellowships and opportunities for North-South linkages.

Research Training

A new administrative procedure, whereby applications for research training grants are solicited once a year and are reviewed by a sub-committee of the Research Strengthening Group (RSG), is now well established and will continue. This allows the RSG to monitor closely the research training component of the Programme and to link these to institution strengthening. Support for Masters-level training is being reduced, except for applicants from least developed countries. In addition, trainees are encouraged to utilize research training opportunities within developing countries to the extent possible.

In order to integrate further developing country scientists in TDR's research and development activities, re-entry grants are reviewed by members of TDR Steering Committees and are managed by Secretaries to the Steering Committees. With the same objective in view, suitable developing country scientists are provided opportunities for training within projects funded under Steering Committees.

Applications for a second round of career development grants will be invited. Applications for these grants, in addition to being judged from a scientific standpoint, will also be assessed for their potential for contributing to institution strengthening, particularly through training of junior researchers.

Research training in general will receive greater emphasis and an increased proportion of funds as compared to previous biennia, and will serve as a major vehicle for research strengthening, particularly for least developed countries. A certain number of grants may be set aside each year for scientists from these countries, since they are likely to be at a disadvantage in competition with scientists working in institutions that have already received substantial institutional strengthening grants. Efforts will be made to interview prospective candidates from least developed countries during initial and subsequent site visits, to identify the most promising. In addition to supporting research training in conventional fields, support will also be provided for training in molecular entomology and appropriate aspects of product development - two areas earmarked by the Programme for development in these countries.

TABLE 5 Programme Area III: Research Capability Strengthening (US\$000)

Component/ Budget Item	1990-1991		1992-1993	
	Approved Budget (1)	Revised Budget (2)	Proposed Budget (3)	Increase (Decrease) (3)-(2)
General Activities				
Personnel Services	1,435.2	1,400.0	1,140.0	(260.0)
Temporary Assistance	100.0	125.0	100.0	(25.0)
Operational Support	700.0	500.0	500.0	0.0
Publications	20.0	20.0	20.0	0.0
Subtotal	2,255.2	2,045.0	1,760.0	(285.0)
Operations				
Institution Strengthening	8,300.0	6,250.0	6,200.0	(50.0)
Training	5,700.0	7,850.0	9,250.0	1,400.0
Subtotal	14,000.0	14,100.0	15,450.0	1,350.0
Epidemiology and Field Research Support (Table 5.1)				
Subtotal	2,650.0	2,125.0	1,940.0	(185.0)
TOTAL	18,905.2	18,270.0	19,150.0	880.0

5.1 EPIDEMIOLOGY AND FIELD RESEARCH SUPPORT

Objectives

- ° Promote and assist field research within TDR, particularly related to field trials of new intervention tools
- ° Strengthen field research capacity in tropical disease endemic countries

Planned Activities 1992-93

Field research is essential in evaluating new tools in a defined epidemiological context. Recognition of the importance of well-designed multi-disciplinary studies incorporating appropriate epidemiological, social science and, where applicable, entomological methods, led to the creation of the Epidemiology and Field Research Support Component in the 1990-91 biennium. This component works closely with the Social and Economic Research Component to promote multi-disciplinary field research.

Epidemiology and Field Research Support has assisted workshops organized under the auspices of disease-specific components to develop outline protocols for field studies on high priority topics not currently addressed by TDR-sponsored research. Multi-disease workshops are also undertaken in which training in planning and protocol development is provided for investigators who have indicated an interest in conducting multi-disciplinary studies. This has resulted in an increase in the number and quality of field projects funded by the disease-specific components of TDR.

The major new initiative is Field Links for Intervention and Control Studies (FIELDLINCS). Its main goal is to establish and sustain multi-disciplinary field research networks to provide support for field-based investigators, through training in project formulation and design, updating methods and techniques of field research, and encouraging project-to-project linkages to standardize criteria and methods, exchange information and facilitate communications. FIELDLINCS will continue to facilitate interchange among field researchers, strengthen their capacity for multi-disciplinary research, provide regular workshops on protocol development, project management, standardization issues, data analysis, and/or specific field research methods, support short term training courses, serve as a focus for multi-centre trials, foster links between field researchers and national disease control programmes, and link those in endemic areas with their colleagues in technically advanced countries in order to contribute to the transfer of skills to endemic areas.

Operational support in the form of equipment or services will be provided to organizations or institutions selected on a competitive basis to serve as resource centres for regional or national networks. An international data base of current field researchers supported by TDR will be updated regularly to complement the FIELDLINCS Programme.

The Epidemiology and Field Research Support Component, in close coordination with the Social and Economic Research Component, will maintain a regular overview of field research throughout the Programme and will participate in the development and assessment of field research plans of other components. It will also develop specific protocols and methods for epidemiological studies, including epidemiological simulation models for selected issues in tropical diseases such as lymphatic filariasis and leprosy. A particular important area will be operational research carried out by or with national disease control programmes in relation to the development of new intervention strategies.

TABLE 5.1 Epidemiology and Field Research Support (US\$000)

Budget Item	1990-1991		1992-1993	
	Approved Budget (1)	Revised Budget (2)	Proposed Budget (3)	Increase (Decrease) (3)-(2)
Operations	1,500.0	1 000.0	1,000.0	0.0
Personnel Services	900.0	950.0	740.0	(210.0)
Operational Support	250.0	175.0	200.0	25.0
TOTAL	2,650.0	2,125.0	1,940.0	(185.0)

6. PROGRAMME AREA IV: PROGRAMME MANAGEMENT

Objectives

- Provide direction, guidance and supervision of all Programme activities
- Support the TDR technical and administrative bodies (JCB, STAC, and Standing Committee) and maintain relations with contributing parties
- Provide financial, personnel, administrative and other management support and services for all Programme activities
- Provide information to governments, scientists, contributing parties and the general public about TDR and tropical diseases

Planned Activities 1992-93

Responsibility for the overall direction, coordination and supervision of the Programme Secretariat rests with the Programme Director, assisted by a small support staff and a Communications Unit. Programme Management includes external relations, financial, personnel, procurement and administrative services and management information and office automation.

External relations activities are the meetings of TDR's technical and administrative bodies and relations with international organizations, governments, non-governmental organizations, foundations and industries collaborating with the Special Programme. Since TDR is dependent on voluntary contributions for most of its income, major emphasis is placed on fundraising and relations with contributors. Activities include the provision of information and periodic visits by the Programme Director and senior Programme staff to contributors and potential contributors.

The Programme's communications activities cover both scientific and technical publications directed primarily to scientific audiences, and more general information about tropical diseases and TDR's activities aimed at the general public and those interested in TDR in governments, organizations, foundations and industry. Major regular communications activities are the biennial Programme Report and the quarterly TDR newsletter. Emphasis will be placed on the provision of relevant and timely information to current and potential contributors, and on making tropical diseases and the role of the Special Programme better known among the general public in contributing countries. Regular contact will be maintained with media representatives in both developing and industrial countries, especially those interested in health matters. The Programme will produce attractive and easily understood publications for general audiences and will make increasing use of audio-visual media.

TDR's computerized management information system provides information on a wide range of Programme activities, especially concerning research proposals submitted to TDR and funded by the Programme. Recent activities have emphasized the expansion of office automation through the introduction of microcomputers for professional and support staff and the development of microcomputer applications for both project management and improved financial management. A major new integrated system, drawing on current applications and databases, and using both mainframe and microcomputers, is under development and should be implemented during 1992-93. This new system will eliminate considerable data duplication among the existing applications, provide greater data consistency and extend the range of computerized information and services available in TDR.

Financial services are directed towards the smooth administration of TDR's finances, including the preparation and revision of programme budgets, control and monitoring of programme expenditures, the recording of contributions to TDR and other TDR income, and the provision of accurate and timely financial reports and analyses. Continued emphasis will be placed on streamlining and simplifying financial systems and procedures, especially through use of computer technology. The implementation of simplified and computerized financial systems in 1989-90 made it possible to reduce personnel requirements in this area.

For the reasons explained in Section 2, Geneva-based costs under General Support, including Administrative Support Services, Premises, Postage and Telecommunications and other Common Services, increased substantially in 1990-91 and small increases are anticipated in 1992-93. The budget provision for Administrative Support Services covers the costs of seven posts in the following WHO units: Accounts (two posts), Budget, Personnel, Records Management, Research Training Grants and Supplies.

The elimination of funding for WHO regional offices (Personnel Services and Duty Travel) reflects a change in the overall financial relations between TDR and the five regional offices whose regional committees include developing countries. Beginning in the 1986-87 biennium, the budgets of these five regions included contributions to TDR to offset the costs of the TDR posts in the regional offices. The contributions were initially equal to 50 per cent of the cost of the posts and were increased to reach 100 per cent in the 1990-91 biennium. This arrangement was reviewed during the preparation of the WHO Proposed Programme Budget for the 1992-93 Biennium and, in the interests of simplifying financial arrangements and clarifying responsibility for the posts, it was decided to terminate the existing arrangements. Thus the responsibility for the ten posts will be transferred to the regional offices as of 1 January 1992. (There will, of course, also be an offsetting reduction in the amount of the WHO contribution to TDR.) Support for duty travel of regional office staff on behalf of TDR will be provided under the budget of the appropriate components, as required.

TABLE 6 Programme Area IV: Programme Management (US\$000)

Component/ Budget Item	1990-1991		1992-1993	
	Approved Budget (1)	Revised Budget (2)	Proposed Budget (3)	Increase (Decrease) (3)-(2)
<i>Personnel</i>				
Personnel Services	2,976.2	3,600.0	3,710.0	110.0
Temporary Assistance	350.0	280.0	300.0	20.0
Consultants/Temporary Advisors	80.0	30.0	50.0	20.0
Overtime	50.0	40.0	50.0	10.0
Staff Training and Development	-	-	20.0	20.0
Subtotal - Personnel	3,456.2	3,950.0	4,130.0	180.0
<i>Operational Support</i>				
Information Systems -				
Equipment & Development	200.0	200.0	150.0	(50.0)
Services & Maintenance	200.0	200.0	200.0	0.0
Public Information	100.0	175.0	100.0	(75.0)
Duty Travel	100.0	140.0	100.0	(40.0)
Office Supplies & Equipment	50.0	25.0	50.0	25.0
Audit Fees	50.0	40.0	50.0	10.0
Subtotal - Operational Support	700.0	780.0	650.0	(130.0)
<i>General Support</i>				
Administrative Support	738.0	1,050.0	1,110.0	60.0
Premises	700.0	600.0	750.0	150.0
Postage & Telecommunications	300.0	300.0	300.0	0.0
Other Common Services	400.0	400.0	450.0	50.0
Subtotal - General Support	2,138.0	2,350.0	2,610.0	260.0
<i>Regional Offices</i>				
Personnel Services	1,002.3	1,002.3	0.0	(1,002.3)
Duty Travel	50.0	50.0	0.0	(50.0)
Subtotal - Regional Offices	1,052.3	1,052.3	0.0	(1,052.3)
TOTAL	7,346.5	8,132.3	7,390.0	(742.3)

7. PERSONNEL REQUIREMENTS

Several developments which affected TDR's personnel situation in the 1990-91 biennium will continue to influence requirements in the 1992-93 biennium. These include the significant increase in personnel costs in 1990-91, which required a careful re-examination of personnel requirements throughout the Programme with a view of effecting savings to the maximum extent. Some savings have in fact proved possible as a result of increased efficiency from office automation and streamlined and simplified procedures. The staffing of the Product Development Component has required significant re-deployment of existing posts from other components. For the reasons explained in Section 6, the ten posts supported by TDR in five of the WHO regional offices will be the responsibility of the regional offices as from the 1992-93 biennium. These posts will therefore be deleted from the TDR budget.

As mentioned in Section 4.2, the *Product Development Component* will have four Professional staff posts (eight staff years) and two General Service staff posts (four staff years). These are all existing posts which have been re-deployed as follows:

- Following the decision to create a separate Component for Product Development, one P post and one GS post which had been approved for product development and biotechnology transfer have been re-assigned from *Research Capability Strengthening*.
- One P post and one GS post, which had previously been devoted to general entomological support in the Programme, have been transferred from *Epidemiology and Field Research Support*.
- One P post which is devoted primarily to diagnostic development, especially in malaria, has been transferred from *Chemotherapy of Malaria*.
- The final P post assigned to Product Development has been established following the disestablishment of a senior GS post in *Programme Area IV, Programme Management* (see also Section 6).

Other personnel changes from the Approved Budget for the 1990-91 Biennium are as follows:

- Following the decision to combine the two previous leprosy components (see Section 4.11), there is a reduction of one P post and one GS post in the new *Leprosy Component*.
- In September 1989 responsibility for the administration of Research Training Grants within WHO was centralized under the Division of Development of Human Resources for Health (HRH). As a result, one senior GS post which had been devoted to this function in *Research Capability Strengthening* was assigned to HRH. This post now appears under *Administrative Support Services* in Programme Area IV, together with the other six posts paid by TDR in a number of WHO support units.
- One other GS post in *Research Capability Strengthening* will be saved as a result of increased office automation in this Programme Area.
- Following the establishment of the integrated chemotherapy development project within the Product Development Unit and other systems improvements, only one GS post will be assigned to support *African Trypanosomiases* and *Chagas Disease*.
- A GS post approved for *Epidemiology and Field Research Support* will be shared between this component and *Social and Economic Research*.
- One other GS post will be saved in *Programme Area IV, Programme Management*, as a result of improved efficiency and re-distribution of workload.

The total number of staff years contained in this Proposed Budget for 1992-93 is 132. There is a total reduction of thirty staff years (or about fifteen posts) from the Approved Budget for 1990-91 to the Proposed Budget for 1992-93 (see Table 7.1). This includes of course the deletion of the twenty staff years or ten posts in the regional offices. The reduction in Programme staff at headquarters is ten staff years or five posts.

TABLE 7.1 Summary of Programme Personnel Requirements

Programme Area	Personnel Requirements In Staff Years			
	1990-1991 Approved		1992-1993 Proposed	
	P	GS	P	GS
I Technical and Administrative Bodies	-	-	-	-
II Research and Development	28	28	32	29
III Research Capability Strengthening	14	18	10	9
IV Programme Management	18	24	18	20
Regional Offices	10	10	0	0
Administrative Support Services	-	12	-	14
Subtotal - Staff Years	70	92	60	72
- Posts	35	46	30	36
TOTAL - STAFF YEARS		162		132
- POSTS		81		66

TABLE 7.2 Personnel Requirements, Programme Area II: Research and Development

Component	Personnel Requirements In Staff Years			
	1990-1991 Approved		1992-1993 Proposed	
	P	GS	P	GS
General Activities	-	4	-	4
Product Development	-	-	8	4
Chemotherapy of Malaria	4	2	2	2
Immunology of Malaria	2	2	2	2
Applied Field Research in Malaria	2	2	2	2
Schistosomiasis	2	2	2	2
Filariasis	2	2	2	2
African Trypanosomiases	2	2	2	1
Chagas Disease	2	2	2	1
Leishmaniases	2	2	2	2
Leprosy	4	4	2	2
Biological Control of Vectors	2	2	2	2
Social and Economic Research	4	2	4	3
TOTAL	28	28	32	29

TABLE 7.3 Personnel Requirements, Programme Area III: Research Capability Strengthening

Component	Personnel Requirements In Staff Years			
	1990-1991 Approved		1992-1993 Proposed	
	P	GS	P	GS
<i>Research Capability Strengthening</i>				
Responsible Officer	2	-	2	-
Medical Officer /Scientist	4	-	2	-
Technical Officer	2	-	2	-
Secretarial Staff	-	12	-	6
<i>Epidemiology and Field Research Support</i>				
Medical Officer /Scientist	6	-	4	-
Secretarial Staff	-	6	-	3
TOTAL	14	18	10	9

TABLE 7.4 Personnel Requirements, Programme Area IV: Programme Management

Component	Personnel Requirements In Staff Years			
	1990-1991 Approved		1992-1993 Proposed	
	P	GS	P	GS
<i>Office of the Programme Director</i>				
Programme Director	2	-	2	-
Secretarial Staff	-	4	-	4
<i>Programme Management</i>				
Responsible Officer	2	-	2	-
External Relations Officer	2	-	2	-
Secretarial Staff	-	4	-	4
<i>Communications</i>				
Communications Officer	2	-	2	-
Editors	4	-	4	-
Secretarial Staff	-	4	-	3
<i>Information Systems</i>				
Management Officer (Information)	2	-	2	-
Programmer/Analyst	2	-	2	-
Clerk/Coder	-	4	-	3
Secretarial Staff	-	2	-	2
<i>Operations and Finance</i>				
Management Officer (Finance)	2	-	2	-
Technical Assistant	-	4	-	2
Secretarial Staff	-	2	-	2
Subtotal	18	24	18	20
<i>Regional Offices</i>	10	10	-	-
<i>Administrative Support Services</i>	-	12	-	14
TOTAL	28	46	18	34