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Scientific review of EORTC trials: the functioning of the New Treatment Committee and Protocol Review Committee

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Abstract

New anticancer treatments (new therapeutic strategies or new compounds) require careful development in which cancer clinical trials are an essential element. Two scientific committees, namely the New Treatment Committee and the Protocol Review Committee, ensure the review of all EORTC protocols with respect to the interest and originality, methodology, feasibility and relevance within the EORTC framework. Both Committees are involved early in the evaluation of the new concept proposal and follow all aspects (methodology, administrative, regulatory) of the protocol development process. Throughout its 25 years of existence, the Protocol Review Committee has streamlined drug and protocol evaluations and has developed standard operating procedures to handle those reviews in a very efficient and fast manner. Since 1997, the New Treatment Committee has contributed to strengthening the EORTC during the development process with the aim of ensuring an optimal flow of information on new drugs between laboratory and clinical research divisions.

Keywords: New Treatment Committee; Protocol Review Committee; Protocol evaluation; Methodology

When the PRC was set up in 1974 under the leadership of Prof. H. Tagnon, the scientific reviews were mainly done by autonomous committee members exhibiting lots of initiative who were left to their own devices, but who occasionally met the chairman to share their enthusiasm for the proposed projects. In 1980, Dr Staquet wrote the first EORTC Protocol Guidelines [1]. Thirty years later, the inaccessible dream has become a reality: the PRC now functions with a meticulously, rigorous, logical approach that is tightly regulated by guidelines. During the next 30 years, one of the primary tasks of the PRC and NTC will be to ensure that these guidelines are sufficiently innovative and progressive to facilitate the discovery and recognition of the value of future treatments. The benefits gained by the patient will continue to be the key to success.

1. The EORTC Scientific Review Committees: a brief overview

1.1. Protocol Review Committee (PRC)

1.1.1. Origin

Although the European Organisation for Research and Treatment of Cancer (EORTC) has been in existence since 1962, there was originally no official scientific committee to which EORTC groups could turn for assistance when preparing clinical trial protocols. The concept of providing appropriate statistical support to the EORTC groups started in 1974 with the establishment of the EORTC Data Center and the Protocol Review Committee headed by Pr H. Tagnon. In 1980, this committee established the first EORTC guidelines for the preparation of cancer clinical trials [1]. During the last 25 years, nine expert clinicians in the field of Oncology trials have occupied this position (Table 1), improving first the quality of the studies and developing standardised and efficient review procedures.

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1.1.2. Role

The Protocol Review Committee is responsible (i) for reviewing studies with respect to their scientific interest and originality, methodology, feasibility and relevance within the EORTC framework and (ii) for assisting the EORTC groups concerning any aspects of the design (methodology) and implementation of all their trials from the first concept idea (outline proposal) to the full protocol and eventual amendments to the protocol. Only protocols reviewed and approved by the Protocol Review Committee may be handled by the EORTC Data Center and bear the EORTC label.

1.1.3. Organisation

Since June 1980, the Protocol Review Committee comprised at least 16 members chosen for their expertise in specific areas. Today, the committee currently counts 24 members. All disciplines of oncology are represented in the review panel. At least 30% of the PRC members do not belong to EORTC Groups, and include one statistician external to the Data Center together with representatives of the US National Cancer Institute. The PRC also makes regular use of voluntary consultants co-opted to advise on specific areas of expertise—a minimum of three and a maximum of five international experts are consulted for each protocol. During the last 2 years, external experts' advice has been geographically balanced mainly between European countries and the US and has also included Japan, Chile and Argentina (Fig. 1). The PRC meets every 3 months at the Data Center to discuss all pending issues, to take the final decision on difficult protocols and to review poorly accruing trials. The PRC chairman is elected by the EORTC general assembly for a 3-year term. All the members comply with the EORTC conflict of interest and confidentiality policies. The external reviewers are requested to keep the information they receive as confidential.

Table 1
Succession of the Chairman from 1974 to 2001[a]

Year period	Protocol Review Committee	New Treatment Committee
1974	H. Tagnon (Brussels)	
1975	M. Hayat (Villejuif)	
1978–1980	C. Jasmin (Villejuif)	
1981–1982	E. van der Schueren (Leuven)	
1983–1984	F.J. Cleton (Leiden)	
1985–1990	J.C. Mc Vie (Amsterdam)	
1991–1993	A. Goldhirsch (Lugano)	
1994–1996	R. Souhami (London)	
1997–1999	M. Aapro (Genolier)	J. Verweij (Rotterdam)
2000	J.P. Armand (Villejuif)[b]	W. Steward (Leicester)[c]

[a] A brief interruption of the EORTC protocols review activities occurred in the 1970s.

[b] Twenty-four Protocol Review Committee (PRC) members were nominated for the period 2000–2002: J.-P. Armand, Chairman, A. Sobrero, Vice-Chairman, M. Aapro, J. Bernier, J-Y. Blay, J. Blazeby, C.F. de Oliveira, T. de Witte, F. Guillemin, E. Jäger, D. Lacombe, F. Meunier, K. Nilsson, M. Parmar, F. Rochard, R. Rosell, H. Sauer, H.J. Schmoll, R. Sylvester, A. Van der Meijden, M. Van Glabbeke, E. Van Limbergen, C. Williams, B.D. Cheson.

[c] Forty-five New Treatment Committee (NTC) members were nominated for the period 2000–2002: W. Steward, Chairman, P. Fumoleau Vice-Chairman, H. Newell, Chairman Laboratory Research Division, L. Eggermont, Chairman Clinical Research Division, O. S. Nielsen, I. Cree, R. Baum, G. Giaccone, I. Judson, U. Keilholz, P. Price, I. Fichtner, V. Bramwell, N. Reed, A. Ravaud, J. Wagstaff, J. Double, M. D'Incalci, A. Ardizzoni, H. Zwierzina, C. Twelves, T. Roberts, P. Woll, E. de Vries, S.D. Fossa, P. Schoeffski, P. Carde, Y. Van Oosterhout, J. Fischer, S. Giacchetti, L. Zitvogel, A. Gesher, C. Sternberg, C. Dittrich, E. van Cutsem, R. Coleman, J.L. Merlin, I. Vergote, C. Focan, N. Brünner, S. Aamdal, A. Spatz, E. Rankin, M. Robinson, J. Verweij.

1.2. New treatment Review Committee (NTC)

1.2.1. Origin

The New Treatment Committee started its activities on 1 October 1997. It emerged from the former New Drug Development Coordinating Committee, which served as a platform for discussion relating to drug development studies performed by the EORTC. Its purpose was to strengthen the development of a comprehensive anticancer drug development programme covering all essential preclinical and clinical stages of drug development (synthesis, screening, formulation, toxicology, phase I and II trials). In 1996, it became evident that there was a similar need to ensure continued support to the EORTC Clinical Research Division. The New Treatment Committee was therefore created with the aims of ensuring the most appropriate internal communication on various aspects of scientific studies, of avoiding any potential for competitive studies within the organisation and EORTC partners and of serving as a forum to provide expertise to further increase the quality of the science within EORTC studies.

1.2.2. Role

The NTC is responsible for reviewing the concept of EORTC trials (outline proposals) that include the use of new, unregistered treatments of malignancies. Its aims include the prioritising of new drugs and modalities offered to the EORTC for development, the review of preclinical data and, where necessary, suggestions for additional preclinical studies. The NTC reviews the available scientific background and determines the potential importance of the new therapeutic modality before granting permission to proceed with protocol development. When appropriate, the NTC attempts to ensure optimal coordination and communication between EORTC groups and the Data Center whenever more than one study is proposed which utilise the same agent/modality. The NTC is also responsible for stimu-

lating translational research within EORTC studies and for ensuring optimal flow of information on new agents between the Laboratory and Clinical Research Divisions. Wherever possible, the NTC ensures appropriate communication of new agent protocols with its EORTC partners. The NTC therefore serves as a Scientific Committee for the EORTC New Drug Development Programme.

1.2.3. Organisation

The EORTC groups propose NTC experts who are ultimately nominated by the NTC chairman in order to achieve a good geographical spread, to balance preclinical and clinical expertise and to cover different areas of expertise. The NTC started its activities with 36 members in 1997–1999 and by 2000 a total of 45 experts with expertise in all treatment modalities involving investigational anticancer approaches had been appointed (Table 1). The specific areas of expertise are in cytotoxic/cytostatic agents, biological agents, anti-hormonal agents, gene therapy, radiotherapy and pathology. The NTC meets once a year jointly with the PRC at the Data Center. This forum is also attended by several observers (NTC guests) including representatives of partner organisations (US National Cancer Institute, Southern Europe New Drug Organisation, Cancer Research Campaign, Arbeitsgruppe Wirkstoffentwickelung Onkologie) who exchange their own experience. In turn, EORTC representatives attend other group meetings (e.g. Cancer Research Campaign phase I-II committee meetings). The NTC chairman is elected by the EORTC general assembly for a 3-year term. All the members comply with EORTC conflict of interest and confidentiality policies.

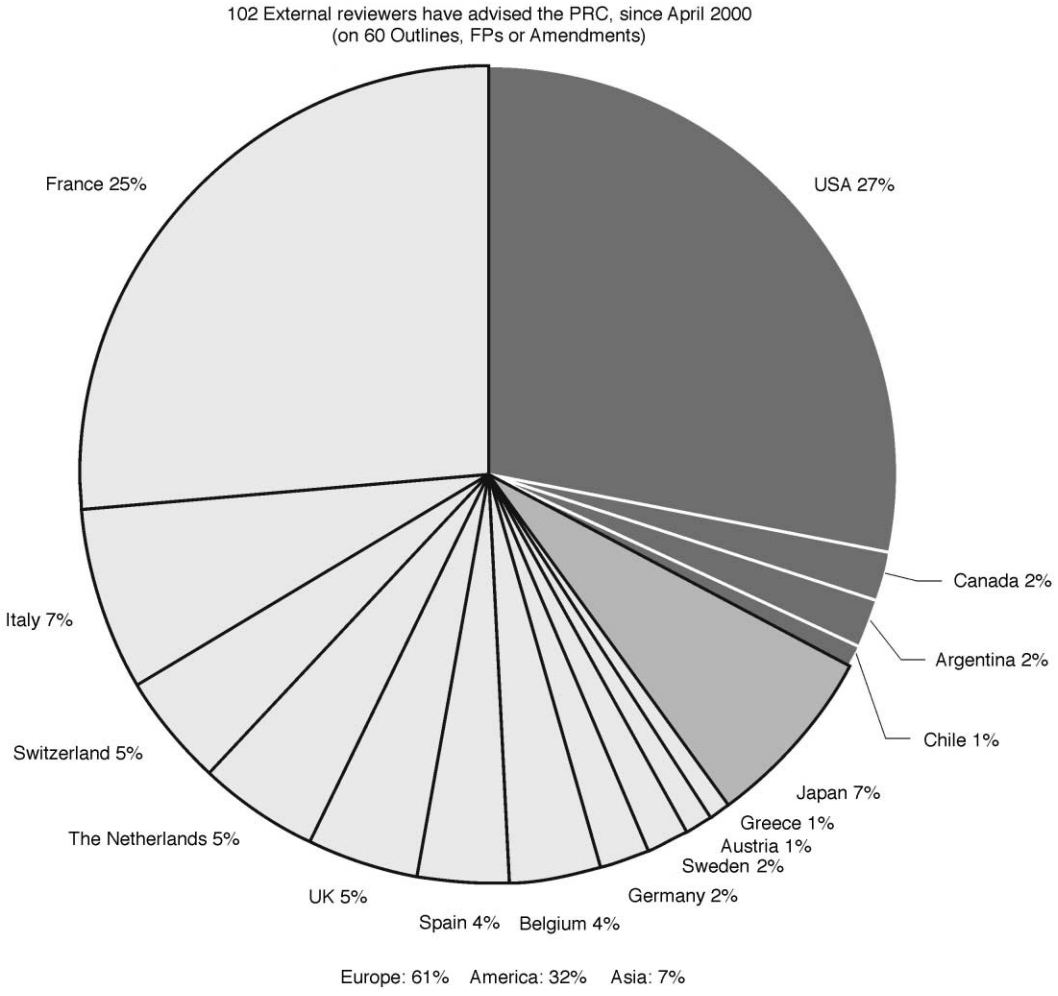

Fig. 1. Contribution of the international consultants co-opted for specific expertise area. The Protocol Review Committee makes regular use of voluntary consultants co-opted for specific problems. Three to five international experts are consulted for each concept outline and on a case-per-case basis for full protocols and amendments to open EORTC trials. Outline proposals with non-registered modalities were not circulated to external reviewers in order to preserve the confidentiality of the project. All the committee members comply with the EORTC conflict of interest and confidentiality policy. The over-representation of the French external reviewer is explained by the origin of the current PRC Chairman (Dr Armand from Institut Gustave Roussy, Villejuif). FP, Full Protocol.

2. Functioning

2.1. Basic principle

The NTC concentrates on new, non-registered, modalities and therefore reviews all phase I and single agent phase II studies, as well as phase II and III studies which include non-registered agents for the studied indication with a focus on the scientific background and the potential for translational research. The PRC reviews all protocols, focusing on the scientific interest of the project, the methodology and feasibility of the study proposal. The usual procedure for referring a protocol to the NTC and PRC starts with the submission of an outline summarising the basic principles of the study. The precise details of the protocol, once the committees give outline approval, are then developed in conjunction with the EORTC Data Center. For the outline submission, the study design is summarised and basic criteria of eligibility, staging, accrual and statistical endpoints should be clearly described. The background should be sufficiently detailed to indicate why the study is felt to be important. If the EORTC PRC and NTC (when applicable) accepts the principles of the study, a trial protocol is then developed and the PRC, as well as the EORTC Data Center, review the final version for methodological issues and coherence. At that point, the principles of the study are no longer questioned, but the details need to be finalised. When more specific expertise is required, NTC experts on behalf of the PRC may also review the full protocol. All the amendments to ongoing EORTC protocols affecting the scientific or ethical content are also reviewed by the PRC and by the NTC (if the proposed modifications are applicable to translational research or relates to new drug development modalities). Finally, some protocols are carried out jointly with non-EORTC oncology national/international groups (so called Intergoup Trials). Intergroup outline proposals where the EORTC contribute to a protocol that will be run by another organisation are evaluated by the PRC in an '*ad hoc*' fashion (take it or leave it, no modifications allowed).

Outlines/full protocols may be accepted at the time of review or more often only accepted after revision, and others are rejected. Most protocol outlines are resubmitted after detailed comments from the NTC-PRC, and could still at that time be reviewed by external experts involved in the particular field. For confidentiality purposes, outline proposals/full protocols regarding non-registered drug modalities are reviewed internally by the NTC and PRC experts, as well as the Data Center, and are not circulated to external consultants (if there are no confidentiality problems, exceptions can be made, particularly when a technology is highly specified and when limited expertise is available, e.g. Boron Neutron Capture Therapy field). If necessary, the outline/full protocol is reviewed at quarterly PRC meetings. In case of conflicts, the study coordinator is invited to discuss concerns raised about her/his proposal in person with the PRC during a quarterly meeting or telephone conference.

2.2. Improvement of the review process

There is always a conflict between the wish of the EORTC groups to get protocols activated quickly and the absolute necessity for the EORTC to ensure that all studies are carried out to the highest standards (scientific, administrative and regulatory) of clinical scientific investigation. Several modifications were instituted in the NTC-PRC functioning in order to meet this important challenge:

1. Trial protocols were initially submitted to the scientific committee only when all scientific matters and administrative details had been finalised. To avoid lengthy procedures for the group and to allow the PRC to fulfil its role at an early step of the protocol development, the PRC implemented in 1992 a two-step review process: first submission of the outline summarising all key issues of the trial and then submission of the full protocol.
2. Initially, all study proposals were reviewed only at the quarterly PRC plenary session, which considerably slowed down the decision process. In 1997, the PRC and NTC jointly implemented a new continuous outline and protocol submission procedure, aiming at minimising the time to decision: outlines/full protocols could be submitted at any time and the PRC meeting became dedicated to review specific issues that needed discussion and consensus between the PRC members. For that purpose, it became evident that the chairmen of the NTC and the PRC should be in extremely close contact. Optimal communication between the two committees was therefore strengthened by the creation of the NTC-PRC secretariat located at the Data Center in Brussels. Having a joint secretariat for both committees optimised the exchange between the NTC-PRC members, the external consultants and the EORTC groups. Importantly, it also means that all protocols can be submitted to the same mailbox at the Data Center. Since the implementation of the new continuous review process, the PRC has had to submit members to a constant flow of outlines, full protocols, and also amendments to the protocols that has considerably increased the burden of these voluntary experts. The need to extend the external consultant network became evident. Between April

2000 and September 2001, 131 external experts have been consulted one or more times for a total of 60 proposals. Approximately 80% of these voluntary experts gave their advice at least once (Fig. 1). The EORTC Review Committees Chairmen would like to express their gratitude to all these collaborating external experts (Table 2).

3. A new feature introduced in 1998 was the electronic submission procedure of outlines via the EORTC Internet web page (http://www.eortc.be) and communication by email between the group, the NTC-PRC secretariat (ntc-prc@eortc.be), the chairmen and the reviewers which also contributed to a further decrease in the review time required in the EORTC.
4. The outline review process has also been streamlined by making NTC and PRC review in parallel. Additionally, all the methodological aspects of each outline proposal are carefully reviewed by the Data Center staff.
5. In order to simplify the review of all administrative issues, but also to guarantee homogeneity of protocols and adherence to EORTC policies, the PRC in conjunction with the EORTC Protocol Help Desk developed standard protocol sections and guidelines for protocol development, which were made available in August 2000 to the EORTC groups. These documents include several standard chapters (insurance, ethical consideration, reporting serious adverse events, randomisation...) guidelines to improve the content/clarity of several scientific chapters (i.e. background, objective, design...) and various templates (i.e. informed consent, data flow...). Currently, all EORTC protocols are built in a modular way with the logistical support of the EORTC Protocol Help Desk that assembles, edits, distributes to the EORTC group the successive versions of the protocol and follows the overall protocol development process. The final version of the protocol is adequately assembled by the Protocol Help Desk in the shortest possible time.
6. Information concerning EORTC protocol procedures has been provided to the EORTC group members. The first general rules to write full protocols were released in 1980 [1] and Newsletters were distributed at the creation of the NTC in order to stimulate exchange of information. The first written EORTC Standard Operating Procedure was developed in 1998 and guidelines for submission of the outlines/full protocols/amendment were made available through the EORTC web site a few months later. These guidelines highlighted all-important steps/requirements and summarised the administrative actions to be performed 'before outline submission', at the time of 'the outline submission' and 'the full protocol submission' and discussed how to handle 'Intergroup studies' 'Amendments' and 'phase II/III studies'. The electronic guidelines as well as the date of the forthcoming PRC and NTC meetings were updated on a regular basis.
7. The importance of rapid responses during the review process has been emphasised. Currently, all members and co-opted consultants are contacted via email and it was agreed that a first decision should be provided within 4 weeks of outline/full protocol submission. This includes 2 weeks for the expert review, 1 week of security margin and 1 week for logistic matters including selection of reviewers and circulation of documents. The NTC-PRC secretariat was strengthened during 2000 to provide additional support for the process and ensure that deadlines are met. Several modifications in the NTC-PRC daily practice were recently implemented in order to achieve the committed 28 days turn-around review time (Table 3).

Table 2
List of External Reviewers who have advised the PRC from April 2000 to September 2001[a]

Abbruzzesse	Cvitkovic	Henriksson	Prentice
Abrams	De Braud	Hensley	Pujade-Lauraine
Agarwala	De Gramont	Hill	Pujol
Alberts	De Haes	Hohenberger	Reichman
Ariyoshi	De Lena	Holland	Roche
Armitage	Delattre	Hudis	Rougier
Armstrong	Demetri	Jakesz	Rubio
Arriagada	Depierre	Kavanagh	Rusch
Bajorin	Diaz-Rubio	Kaye	Scalliet
Barbui	Diehl	Kirkwood	Schiller
Benjamin	Dietrich	Lauraine	Seidman
Block	Dixon	Levi	Shepherd
Blum	Donat	Levin	Shimada
Bosl	Droz	Lhomme	Spiliopoulos
Bottomley	Durand-Zalevski	Louvet	Standaert
Bourhis	Escudier	Marty	Studer
Brada	Fizazi	Mattson	Tannock
Bunn	Fossella	Merlano	Thalmann
Capala	Fourquet	Middleton	Tirelli
Cazap	Gahbauer	Mignot	Tonato
Cella	Georgoulias	Misset	Turrisi
Chopin	Gianni	Montie	Velu
Cognetti	Gisselbrecht	Ozols	Verhoef
Coiffier	Goemine	Paridaens	
Cortes-Funes	Gramont	Pavlovsky	
Curt	Grunenwald	Penault-Llorca	

[a] The EORTC Review Committee's Chairmen would like to express gratitude to the 102 international experts (medical oncologists, radiologists, surgeons, health economic specialists, quality of life specialist, etc.) who contributed, on a voluntary basis, to improve the science in a large number of EORTC proposals. The majority of the above-listed external reviewers are not involved in EORTC activities, while some of them are EORTC Members collaborating with different treatment-oriented Groups.

3. Timeliness

3.1. Commitments

Based upon the present experience and despite the busy practice of all the NTC and PRC members, it can be stated that the review time for the committees within EORTC is quite short and meets the median of 28 days turn-around, the criterion established in 1998. In addition, we are happy to note that the addition of the new NTC scientific panel did not extend the review process. After the approval of the study concept, the full protocol developed accordingly the EORTC standard methodology should be submitted within a 6-month period to the PRC in order to keep high scientific value and interest and to guarantee a rapid activation of the trial. The first decision is communicated to the group within 4 weeks. Priority is given to open trials, and therefore the amendment proposal receives a decision within 2 weeks. Exceptions are made for some complex major modifications to the trial design, eligibility, treatment schedule/dosing, etc., which need extended review.

3.2. Current achievements

In 2001, the PRC reviewed 31 outline concepts, of which 18 have been jointly reviewed with the NTC. The mean time to achieve a first decision was 26 days (range 21–42 days) for the NTC and 31 days (range 17–48 days) for the PRC, depending on the complexity of the concept proposal which largely differ according to the type of trial (phase I versus phase III). Over the same period, the committees accepted 17 outlines proposals (2 phase I, 6 phase II, 8 phase III, 1 quality of life) and rejected eight projects (3 phase II, 5 phase III). The groups have withdrawn two outlines, while four study proposals were still under discussion and should be resubmitted for final decision. Additionally, the PRC reviewed 31 full protocols (2 phase I, 11 phase II, 3 phase II/III, 12 phase III, 2 quality of life, 1 survey) with a mean review process time of 34 days (range 14–61 days). Approximately 60 amendments have also been reviewed.

4. Conclusions

For the purpose of strategic trials or to develop new molecule-based therapy, the establishment of a Protocol Review Committee within the EORTC was essential to ensure the development of clinical protocols, which were scientifically sound, incorporated the appropriate methodology and fulfilled the requirements for quality control of the EORTC. With growing awareness of the importance of developing new treatment strategies, an increasing number of phase I and II trials have been developed through many of the disease-oriented groups. The creation of the NTC has helped to meet the needs for new drug development programme within the EORTC and complements the existence of the PRC. A

Table 3
Recent improvements in the daily practice of the NTC-PRC to speed up the review process

Objectives	Action taken	Date implementation
To shorten time to select reviewers	• To improve selection process: new PRC expertise form	December 2000
	• 'Selection of PRC members' proposed by the NTC/PRC Secretariat (informed on the availability, expertise, document already sent)	December 2000
To improve feasibility	• To ask to confirm feasibility as soon as possible	October 2000
	• To send a reminder 2 days before deadline	Was already applied
	• 'Monitoring' the participation and the frequency of request.	October 2000
	• To reduce delay for review from 3 weeks to 2 weeks	March 2001
	• 'Monitoring' unavailability during summer period	July 2001
To reduce the workload	• To ask only 2–3 PRC members and 2–3 NTC members	October 2000
	• To send 'standard e-mail' detailing what chapters of the FP need to be reviewed	November 2000
	• To ask NTC experts to review FP	December 2000
	• To delegate review of Group Specific Appendix to the EORTC Intergroup office in cases of intergroup trials.	April 2001
To improve 'decision process'	• To design a new PRC 'outline evaluation form' (grading of the study, availability to review FP, guidelines for the decision)	April 2001
	• To design a new 'FP evaluation form'	April 2001
To reduce 'delay in FP submission'	• 'Monitoring' the reason of delay in FP submission	February 2001
To increase PRC and NTC expertise	• Collaboration of two new members in both committees	November 2000
To shorten 'administrative delay'	• To increase manpower at the NTC-PRC Secretariat	July 2000

FP, full protocol; NTC, New Treatment Committee; PRC, Protocol Review Committee.

large number of experts are available to review protocol outlines and final protocols.

The need for rapid review of proposals was accepted by the NTC and PRC and, as a result, several changes have been made to the process of review. The EORTC has provided significant increases in the infrastructure with the creation of the Protocol Help Desk and, of great importance, the creation of the NTC-PRC Secretariat. A turn around time of 28 days has been achieved for almost all of the protocols. As a result, the EORTC is confident that the process of protocol creation incorporates a high degree of quality assurance with feedback from experts in the field involved and that this is performed in a timely fashion which has a minimal impact on the institution of new trials.

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