NCI Clinical Trials and Translational Research Advisory Committee (CTAC)

National Clinical Trials Network (NCTN) External Evaluation Working Group Report

This report was accepted by the Clinical Trials and Translational Research Advisory Committee at its meeting on March 8, 2017

NATIONAL CANCER INSTITUTE
CLINICAL TRIALS AND TRANSLATIONAL RESEARCH ADVISORY COMMITTEE (CTAC)
NATIONAL CLINICAL TRIALS NETWORK (NCTN) EXTERNAL EVALUATION WORKING GROUP

WORKING GROUP REPORT, MARCH 8, 2017

EXECUTIVE SUMMARY

The National Clinical Trials Network (NCTN) External Evaluation Working Group (NEE WG) was tasked with assessing the value and impact of the NCTN in order to determine whether the program should be renewed. After considering the scientific impact of the NCTN program as well as feedback from the Group Chairs and NCTN Group stakeholders, the Working Group recommends that the program be continued. This report contains the evidence for that recommendation as well as recommendations for near-term and longer-term improvements of the NCTN, including topics for further analysis.

INTRODUCTION

Established on March 1, 2014, the NCTN, part of the National Cancer Institute's overall clinical research program, conducts treatment and imaging trials, including definitive phase III trials, randomized phase II trials exploring new ideas, and precision medicine trials. The NCTN was created to address the challenges of precision medicine, which include screening large numbers of patients to identify those whose tumors contain the distinct molecular targets of the therapies being tested. The NCTN is organized to take maximal advantage of the opportunities afforded by the improved understanding of tumor biology. The centralization and streamlining of many critical functions, such as tissue banks, ethics approvals, and imaging support enhance its effectiveness. The NCTN was designed to improve the speed and efficiency of cancer clinical trials. It includes the following components:

1. NCTN Network Group Operations Centers
2. Canadian Collaborating Clinical Trials Group
3. NCTN Network Group Statistical and Data Management Centers
4. NCTN Lead Academic Participating Sites (LAPS)
5. NCTN Imaging and Radiotherapy Oncology Core Services (IROC)
6. NCTN Integrated Translational Science Awards (ITSAs)

Two core questions were posed to the Working Group:

1. Is the NCTN program of sufficient value to recommend that NCI proceed with consideration of renewing the program?
2. Are there any major recommendations for enhancing the scientific direction and/or operations of the overall NCTN and/or the individual NCTN components?

In addressing these questions, the Working Group was asked to consider four areas of evaluation:

1. Overall value and scientific impact of NCTN clinical trials and other activities
2. Effort integration and collaboration across the NCTN
3. Overall timeliness of clinical trial development, accrual rates and efficiency of operations
4. Interactions with other federal and non-federal organizations and programs

NEE Working Group members (listed in Appendix 1) were chosen for their knowledge of NCI's late phase trials program, and were determined to be free from conflicts of interest related to the NCTN. In preparation for the evaluation, members reviewed the source materials listed in Appendix 2. NCI clarified that the evaluation would not cover specific diseases, individual trials, or the funding for individual NCTN component grantees. At the face to face meeting on January 26, 2017, NCI provided its perspective on the NCTN. Next a summary of the stakeholder survey results, the Group Chairs' comments and the feedback from the Group meeting town halls was presented. Then members assigned to the four areas of evaluation presented the strengths and weaknesses of the NCTN drawing on the evaluation source materials. Based on this information, the Working Group recommended the continuance of the NCTN. The Working Group then articulated the evidence in support of renewing the NCTN and developed recommendations on opportunities for near-term and longer-term NCTN improvement and NCTN-related topics that warrant further analysis.

OVERALL RECOMMENDATION

The NCTN External Evaluation Working Group recommends that the NCTN program be continued.

EVIDENCE IN SUPPORT OF NCTN CONTINUTATION

Working Group members concluded that the following, organized by the four areas of evaluation, constituted the most important evidence in support of NCTN continuance.

OVERALL VALUE AND SCIENTIFIC IMPACT

Under the NCTN, highly significant, practice-changing trials have been conducted or are in progress, many of which could not have been conducted without public funding, for example

- Difficult randomized comparisons of types of radiotherapy, surgery or drug treatment versus no treatment,
- Studies of combined modality therapy,
- Studies evaluating agents from different companies (either alone or in combination),
- Evaluations of inexpensive commercial agents,
- Studies where NCI supplies the manufactured drug,
- Studies designed to reduce the need for surgery or radiation,
- Studies of unique surgical approaches, such as laproscopic resection of rectal cancer,
- Studies in rare tumors,
- Studies in pediatric cancers, and
- Studies with behavioral interventions, such as for breast cancer recurrence

Widely considered a major accomplishment, the NCTN has demonstrated the unique ability to conduct precision medicine trials, such as LUNG-MAP[1], ALCHEMIST, MATCH, and DART, which would not have been feasible under the previous Cooperative Group system. The coordinated structure of the NCTN enables accrual of the large numbers of patients nation-wide that is required for these trials. In addition, the Groups have successfully collaborated with NCI to resolve some initial issues with implementing precision medicine trials, including providing additional funds to cover the extensive screening effort required and addressing logistical problems such as assay result turnaround times.

In addition to incorporation of precision medicine trials, the NCTN also has increased its emphasis on smaller phase II studies which, because they are focused on underlying biological principles as opposed to changing clinical practice, may lead to major advances in the future. Furthermore, the extensive public-private partnerships and the coordination of studies with industry were viewed as expanding the NCTN trial repertoire. These strengths are reflected in the fact that in the NCTN stakeholder survey, 72 percent of respondents consider NCTN trials to meet or exceed expectations in terms of incorporating innovative science.

EFFORT INTEGRATION AND COLLABORATION ACROSS THE NETWORK

Improved integration and collaboration was a central goal in restructuring the former Cooperative Group program to form the NCTN. In terms of NCTN operations, several items were noted by the Working Group as having contributed to a more integrated network. These include: universal adoption of the Cancer Trials Support Unit (CTSU) Regulatory Support Services (RSS) and the OPEN centralized patient enrollment system; development of an integrated site roster across NCTN and NCORP; creation of NCTN Archive, a de-identified patient-level database from completed trials, to enhance data sharing; and implementation of the Medidata Rave data management system for all new trials. In addition, as of November 1, 2016, over 80 percent of US institutions in the NCTN are enrolled in the NCI Central Institutional Review Boards (CIRBs). Per-case funding for data management at sites has also been harmonized so that sites will know exactly how much funding to expect for a given study.

One important change for the NCTN is that any site can accrue patients to trials of all Groups, not just to trials of the Group(s) to which they belong. In the prior Cooperative Group program, trials were not open to everyone. In terms of collaboration in accrual across the adult Groups, the average accrual to a trial led by one Group from members of other Groups is 33.6 percent, although there is substantial variation across the Groups (SWOG 51.5 percent, Alliance 40.1 percent, ECOG-ACRIN 33.4 percent, and NRG 9.5 percent). The Working Group noted that it was not surprising that NRG trials have the lowest cross-Group accrual given that many of their trials are of interest to physicians with a specialty interest (e.g. gynecologic oncology) or involve radiation therapy, which appeals to a limited set of institutions. Working Group members also noted that cross-Group accrual data need to be interpreted carefully. Many Cancer Centers and NCORP Sites are members of multiple Groups and therefore are accruing across Groups even if they always credit their accrual to a specific trial to the Group leading that trial. With regard to screening accruals to precision medicine trials, the evidence for cross-Group accrual is similar in that approximately half of the accrual is from the Group leading the trial and the other half is from other Groups. The NCTN has also facilitated the development of trials for adolescents and young

[1] Abbreviations are listed in Appendix 3

adults involving both COG and the adult Groups. Prior to the NCTN, there were few trials for this population in part because they were too difficult to implement.

In terms of accrual by NCTN site role, for 2014-2016, the 30 LAPS contributed an average of 27 percent, the 46 NCORP sites 32 percent, and the Rostered Group Members 41 percent, which is a fairly even distribution. However, over the three years, while the percent accrual from the LAPS has remained constant, the percent accrual contributed by NCORP sites has increased and that by Rostered Group Members has decreased. Finally, NCTN overall accrual is widely distributed across the U.S., roughly reflecting population density.

In terms of collaboration beyond accrual, four items are worth noting. First, 31 of the trials highlighted by the Groups as accomplishments involve not only cross-Group accrual but also substantive cross-Group collaboration in study development and/or management. Second, over 70 percent of stakeholders consider the various entities established to support the activities of the Groups, including the LAPS, IROC, Tissue Banks, NCORP, and CCTG, to meet or exceed expectations, which implies effective integration of these entities with the Groups and the overall NCTN. Third, 74 percent of stakeholders consider collaboration across specialties and disciplines within the NCTN to meet or exceed expectations. Finally, several committees have been established to provide collaborative management of the NCTN by the Groups and NCI. These include the NCTN Leadership Management Committee, the IROC Executive Committee, and the NCTN Core Correlative Science Committee.

TIMELINESS OF TRIAL DEVELOPMENT, ACCRUAL EFFICIENCY, AND EFFICIENCY OF OPERATIONS

With regard to accrual efficiency, the yearly accrual under the first two years of the NCTN is similar to accrual in 2012 and 2013 before the NCTN was formed and reflects the total accrual that the NCTN budget can support. The average "screening-on-study"[2] accrual (4,168 patients per year) substantially exceeds the NCTN target of 2,500-3,000 patients per year which reflects the enthusiasm for and the increased number of molecular marker driven trials. In light of the more specific eligibility required by these trials, the average intervention accrual for 2014-2016 (16,430 patients per year) is slightly below the NCTN target of 17,000-20,000 patients per year, so that the total accrual remains comparable to prior years. In terms of the timeliness of trial development, the Working Group noted that new phase II and phase III trials launched by the NCTN continue to fall within the absolute deadlines for the time from concept approval to protocol activation, as recommended by the Operational Efficiency Working Group. They encouraged NCI and the Groups to work to further reduce the time it takes to activate a study.

In terms of operating efficiency, the CTSU, the CIRBs, and the Medidata Rave system are viewed by 84 percent of the NCTN stakeholders surveyed as meeting or exceeding expectations. Operating efficiency is also likely to be further improved by new initiatives to coordinate audits and provide central remote monitoring of key trial data as well as electronic registration of investigators.

[2]"Screening-on-study" accrual means patients who are screened for a specific trial but not necessarily enrolled (in cases where they don't have the required marker for the study.)

INTERACTIONS WITH FEDERAL AND NON-FEDERAL ORGANIZATIONS AND PROGRAMS

The NCTN has enabled Groups to better coordinate with industry partners as well as academic, international, and other federal entities. As of October 31, 2016, there were 9 NCTN registration/licensing trials open involving 7 different agents and 6 pharmaceutical companies. Moreover, a number of important NCTN trials, including MATCH, LUNG MAP, and TailoRx, involve collaborations with industry. In addition, over 200 externally funded grants (R01, R21, DoD, LLS, ACS) have supported translational studies embedded in NCTN trials or using NCTN biospecimens.

The NCTN also has other notable external interactions including with the Biomarkers Consortium of the Foundation for NIH and Project DataSphere, an initiative of the CEO Roundtable on Cancer's Life Sciences Consortium which provides a free digital "library-laboratory" of patient-level data from academic and industry phase III trials. The NCTN also has important international collaborations such as EURAMOS. Funding for NCTN trials comes from many sources including federal agencies, foundations, other not-for-profits, professional societies, international foundations and governmental/quasi-governmental entities, pharmaceutical companies, device companies, and clinical laboratories.

RECOMMENDATIONS FOR NEAR-TERM NCTN IMPROVEMENT

Working Group members made 13 recommendations suitable for incorporation in the upcoming renewal of the NCTN program.

RECOMMENDATIONS RELATED TO SCIENTIFIC IMPACT

1. NCTN goal statement should be revised

The 2012 NCTN goal statement[3] should be revised in two ways. First, the goal should reflect that NCTN trials have an impact on human life by including text such as "*reducing the morbidity and mortality of cancer for adults and children and improving patient outcomes"*. Second, because not all NCTN trials are "randomized" and "definitive", the goal should be broadened to include other trial categories and not just "late-phase" trials.

2. NCTN portfolio should emphasize science-driven phase II and phase III trials

There is currently an approximately equal balance between phase II and phase III trials in the NCTN portfolio. This represents a shift from the previous Cooperative Group program, in which phase III trials made up more than 80 percent of the portfolio. The NCTN has also placed a strong focus on precision medicine trials, which were not part of the prior program. The NCTN should continue to have both phase II trials exploring innovative new ideas and clinically impactful phase III trials. The NCTN should be

[3] Goal of NCTN Program (from 2012 RFAs): The overall goal for the entire NCTN Program is to conduct definitive, randomized, late-phase clinical treatment trials and advanced imaging trials across a broad range of diseases and diverse patient populations as part of the NCI's overall clinical research program for adults and children with cancer.

continuously poised to undertake those biology-based, innovative studies that would unlikely be conducted through other mechanisms including industry.

3. NCTN portfolio should include trials across modalities

Working Group members noted that surgery, radiation, and imaging studies tend to be isolated, small components of the NCTN portfolio which leads to the perception that these non-drug studies are less important for the NCTN. To reduce this perception, the NCTN should state explicitly that high quality trials of agents, surgery, radiation, and imaging modalities are all of high interest.

4. Groups should identify areas of scientific excellence and expertise

Although Working Group members noted that overlap in the scientific interests of the NCTN Groups leads to the development of a diverse range of trial ideas, some members commented that it would also be beneficial for different Groups to occupy somewhat distinctive scientific niches which could reduce competition and overlap in trial development activities. Therefore, the Working Group recommended that the Groups articulate in their NCTN applications a few areas in which they have specialized expertise and experience and which they propose to emphasize with regard to trial development.

RECOMMENDATIONS RELATED TO COLLABORATION WITHIN NCTN

1. Groups and NCI should enhance strategic scientific collaboration

Working Group members expressed the view that improved collaboration in setting the scientific direction for the NCTN would be beneficial. Therefore, the Groups should more optimally collaborate both with each other and with NCI to identify the most important strategic issues in cancer treatment both for individual diseases and across diseases. The identified issues should then be used by the Groups to guide trial development.

2. Groups should maintain a high level of cross-Group collaboration in accrual and study development

A major part of the vision for the NCTN is collaboration among Groups, including but not limited to robust cross-Group accrual. The Groups should therefore maintain and hopefully improve the current level of cross-Group accrual for trials of interest to multiple Groups. Working Group members noted that achieving a higher level of cross-Group accrual will require overcoming the mindset wherein Group members primarily accrue to trials led by their own Group, a holdover from the Cooperative Group program. However, as noted previously, many Cancer Centers and NCORP sites are members of multiple Groups and therefore are accruing across Groups even if they credit their accrual to the Group leading that trial.

Working Group members also noted the importance of greater cross-Group collaboration in trial development. Collaborative trial development would reduce wasted effort when different Groups develop competing trial concepts and potentially lead to more robust and impactful trials. However, the Working Group acknowledged that because each of the Groups must undergo individual peer review, to achieve improved collaboration, it will be important that collaboration in trial development is as important a criterion in review as the development of individual trials.

3. Coordinated management of the NCTN should be further strengthened

Several forums have been established to enhance coordinated management of the NCTN including the Leadership Management Committee, the IROC Executive Committee, and the Core Correlative Science Committee. Going forward, the Groups and NCI should commit to making these forums, especially the Leadership Management Committee, not only useful for exchanging information but also for open discussion and joint resolution of strategic management issues facing the NCTN.

4. Groups should encourage intra-Group disciplinary and operational integration

Working Group members expressed the view that Groups would benefit from more extensive collaboration across disciplines both in terms of cross-disease collaborations to take advantage of pathway-driven science and development of trials integrating multiple modalities. Therefore, the NCTN should more explicitly encourage such collaborations. In addition, because greater operational integration is likely to improve efficiency and cost-effectiveness, Groups should be asked to describe in their applications initiatives they have either implemented or are planning to implement that will enhance integration of their operating functions. This will be especially important for Groups that represent a consolidation of two or more previous Cooperative Groups.

5. Groups should clearly define the roles and responsibilities of patient advocates in Group activities

Working Group members emphasized the importance of involving patient advocates in the generation and vetting of new trial ideas as well as in the review of concepts and protocols to ensure that the questions addressed are likely to be of interest to patients. The concern was also expressed that there was wide variation in the involvement of advocates in these activities across the different Groups and even within Groups. Therefore, the Groups should be asked to describe in their applications both current and planned approaches for engaging patient advocates in Group activities, some of which might represent best practices that could be shared across the Groups. In addition, NCI should consider expanding the training provided to advocates who serve on Steering Committees and Task Forces in order to develop a pipeline of trained individuals who can participate in both Group and NCI efforts.

RECOMMENDATIONS RELATED TO EFFICIENCY

1. Groups should improve internal trial development timelines

Working Group members expressed major concerns about current study development timelines. The target protocol development timeline for early-phase trials post concept/LOI approval is 210 days, but the median is 441 days, close to the absolute deadline of 450 days. The target timeline for late-phase trials post concept approval is 300 days, but the median length is 529 days, again close to the absolute deadline of 540 days. The Working Group suggested that NCI could consider shortening the absolute deadline to force more rapid protocol development, but acknowledged that understanding and correcting the sources of delay was a more reasonable approach. Working Group members also noted that there may be substantial delays in the concept/LOI development process within Groups, which are not currently tracked on an NCTN-wide basis. In order to increase attentiveness to the timeliness of trial development, Groups should be asked to provide in their competitive renewal applications current internal timelines for each step in both concept/LOI development prior to Steering Committee or CTEP

evaluation as well as in protocol development post concept/LOI approval. They should also be asked to describe actions taken to reduce the time required for lengthy steps as well as plans for further timeline improvements including standardizing processes across their committees. Ideally, best practices will be developed and shared among the Groups.

2. Groups should support leadership training and promote diversity in Group leadership

Working Group members noted that while Group Chairs and Committee Chairs are expert scientists, they may or may not possess the leadership and/or mentoring skills that are critical for effective Group and Committee management. Additionally, members had concerns about diversity in Group leadership in terms of age, gender and academic versus community oncologists. Therefore, Groups should be asked to describe in their applications planned leadership training for Group and Committee Chairs and approaches for achieving diversity in age, gender and academic/community oncology representation in Group leadership including providing opportunities for young investigators to lead trials and assume higher-level roles within the Group. The proposed initiatives should also be evaluated to determine if they represent best practices that could be shared across the Groups.

3. Groups should emphasize and facilitate minority/underserved accrual

Accrual from minority populations has remained virtually unchanged during the three years of the NCTN compared to the three years prior to the NCTN at approximately 15 percent non-white and approximately 10 percent Hispanic/Latino. Working Group members expressed concern about the level of minority accrual especially since it has not changed since 2011. The Working Group was also provided with a "heat-map" which showed the level of NCTN accrual in each State as a percentage of the incidence of new cancer cases in that State. This demonstrated that the percentage was especially low in states where cancer incidence is high and there are large minority populations, such as Mississippi, Florida, Alabama and Tennessee. Therefore, it is important for Groups to develop and describe in their NCTN applications initiatives to increase emphasis on and facilitation of minority/underserved accrual and to track success of the proposed initiatives.

RECOMMENDATION RELATED TO EXTERNAL COLLABORATION

Although the NCTN does have a large number of collaborations with other federal entities, commercial companies, and international clinical trials organizations, the Working Group members expressed a concern that NCI is sometimes perceived to not be supportive of those collaborations. This was especially noted in terms of international collaborations and collaborations with PCORI, DoD, FDA, and other NIH Institutes. Therefore, NCI should make more explicit that it is supportive of collaborations with external partners in the development and conduct of NCTN trials, including working with industry and the FDA on registration-level trials. NCI should also improve facilitation of these collaborations and provide specific guidance on the types of situations when such collaborations might not be feasible or desirable from NCI's perspective. The Working Group also noted the importance of the collaboration with NCORP and encouraged its continuation.

RECOMMENDATIONS FOR LONGER-TERM NCTN IMPROVEMENT

In addition to the near-term recommendations described above, the Working Group made two recommendations which are much longer term in nature and cannot be accomplished in association with the upcoming renewal of the NCTN and should be considered for inclusion in subsequent NCTN renewals.

1. Evaluation of certain NCTN features

The Working Group concluded that it was too early to evaluate certain features of the NCTN because they were initiated in association with the launch of the NCTN and therefore have been in operation for less than three years. These features include the ITSAs, the LAPS and the credentialing standards implemented by IROC, all of which the Working Group recommended be specifically evaluated prior to a subsequent NCTN renewal.

2. Development and implementation of best practices across the Groups

The Working Group noted that because all Groups are performing similar operational activities, it might be beneficial to identify best practices developed by one or more Groups for dissemination and implementation across the NCTN. However, the members recognized that the process of identifying and reaching consensus on such best practices would likely require considerable time and effort. Therefore, the Working Group recommended that NCI and the Groups begin in a timely manner an investigation with the goal of being in a position to recommend implementation of certain best practices NCTN-wide in time for a subsequent program renewal.

SUGGESTED TOPICS FOR FURTHER ANALYSIS

In addition to the recommendations related to reissuance of the NCTN program, the Working Group identified six topics that were either outside their charge or that needed more in depth consideration. The members thought these topics were of sufficient potential impact on the NCTN to warrant further consideration by CTAC or NCI.

ANALYSIS TOPICS FOR CTAC

1. Scientific Steering Committee operating processes

Although not directly within the scope of the NCTN evaluation, Working Group members raised a number of issues concerning the Scientific Steering Committees, which evaluate and approve concepts for NCTN late-phase trials. Raising of these issues was not surprising given the degree to which the Steering Committees are interwoven with the NCTN study development process. One issue discussed was the need for greater alignment of and communication about Steering Committee processes and review criteria and Group processes for trial development. Working Group members expressed the view that improvement in these areas would help minimize investment by the Groups in development of concepts that will be difficult or impossible for the Steering Committees to approve. It was also mentioned that approaches for early communication between the Groups and the Steering Committees about the innovation and impact of trial ideas on cancer morbidity and mortality might also be beneficial in this regard. A second issue was that the mechanism for prohibiting or discouraging development of competing trial concepts was perceived as in need of improvement. A final issue noted

was the variation in operating processes across the Steering Committees. It was suggested that identification and implementation of Steering Committee best practices might be beneficial for improving efficiency and consistency. Recognizing that these issues were important to address but not directly within their purview, Working Group members recommended that CTAC undertake an analysis of Scientific Steering Committee operating processes in addition to the planned strategic scientific assessment by the CTAC Clinical Trials Strategic Assessment Working Group.

2. Integration of translational research with NCTN trial development and conduct

Working Group members raised a variety of questions concerning the degree to which advances in translational research are integrated with the development of NCTN trial ideas by the Groups. The Working Group was provided with a description of the activities of the Integrated Translational Science Awards (ITSAs) but because these projects are just beginning it was difficult to assess their impact on future NCTN trials. In addition, it was beyond the scope of the Working Group to assess the degree to which translational advances by non-NCTN programs such as SPOREs are incorporated into NCTN trial development activities. A related topic was the concern expressed about the difficulties of incorporating correlative studies into NCTN trials or even performing correlative studies on specimens from NCTN trials as the funding for such studies must come from non-NCTN sources. Although Working Group members considered the integration of translational research with the development and conduct of NCTN trials to be critically important for making major advances in the development of innovative cancer treatments, they recognized that this was beyond the scope of their deliberations. Therefore, they recommended that CTAC undertake an analysis of this issue which could include the degree to which ITSA and SPORE projects are strategically integrated with the needs of future NCTN trials (e.g., directed at the same high priority clinical questions) and approaches for overcoming the challenges associated with incorporating correlative studies into NCTN trials.

3. Basis of NCTN stakeholder concerns

The NCTN stakeholder survey and the input solicited by the Working Group from the NCTN Group Chairs identified two concerns that the Working Group considered sufficiently important to warrant recommending that CTAC undertake an analysis of their extent and basis. The first concern was that less than 50 percent of NCTN stakeholders responding to the survey considered the number and "menu" of NCTN trials to meet expectations. The term "menu" was not defined in the survey so one of the goals of a CTAC analysis would be to understand the exact nature of the low satisfaction with the "menu" of NCTN trials. The second concern was the balance between CTEP's and extramural investigators' roles in the management of operational and scientific activities of the NCTN. The goal of a CTAC analysis would be to determine whether these concerns are perceived or actual, the basis for the concerns (whether perceived or actual) and approaches for addressing the concern or better communicating so a misperception does not continue to exist.

4. Transitioning community sites from phase III to precision medicine and phase II trials

The Working Group noted that the shift in NCTN emphasis from large (and often easier to conduct) phase III trials in common diseases toward innovative precision medicine and phase II trials in rare genotypic or phenotypic populations creates additional challenges for community sites. The challenges include more demanding and variable technical requirements, trials that are more complex to explain to patients and ultimately trials that will be available to smaller numbers of patients. Unfortunately, these

challenges may begin to undermine part of the value for community site participation in NCTN trials because, in the end, fewer of their patients will be offered participation in clinical trials. The Working Group therefore suggested that CTAC undertake an analysis of the optimal role for community practices in the new NCTN model and recommend approaches for continuing to meet NCTN objectives and still provide value to community practices commensurate with the substantial pro-bono contribution required for NCTN participation.

5. NCTN accrual efficiency

The Working Group was only provided data on accrual efficiency (actual versus originally expected accrual rates) for the 14 phase III trials activated after March 2014 and open for at least 12 months. This represents only a small subset of the approximately 70 NCTN phase III trials that accrued patients since March 2014. There was no data provided on the accrual efficiency for phase II trials. Given these limited data, it was impossible for the Working Group to evaluate the efficiency of NCTN accrual on a trial by trial basis. However, Working Group members expressed the view that accrual often lags behind that expected when the trial was launched and studies thus take too long to complete.

Because timely completion of trials is key to advancing cancer treatments for overall patient benefit, the Working Group suggested that CTAC undertake a comprehensive analysis of accrual efficiency by examining the actual versus originally expected accrual rates on a trial-by-trial basis for all NCTN phase III, phase II/III and phase II trials that are actively accruing patients. This analysis would provide information on the extent of the problem (e.g., percentage of trials substantially behind their originally expected accrual rates, degree to which study completion times are extended due to slow accrual) as well as the specific trials which are slow accruing. These trials could then be examined for common themes or factors that slow accrual in order to develop recommendations on ways to identify in advance trials that are likely to be slow-accruing so that either trial designs can be modified to reduce accrual barriers or specific interventions implemented to promote accrual. The Working Group noted, however, that in assessing accrual efficiency for international trials if U.S. participants do not meet their own target accrual, this should not necessarily be viewed as a negative because if the global accrual is completed efficiently then the U.S. site has still made a meaningful contribution to that efficiency.

ANALYSIS TOPIC FOR NCI

Working Group members identified insufficient funding for the NCTN as a major concern. Five areas were especially highlighted. The first was per-accrual funding particularly given the increasing technical complexity of NCTN trials. Concern was also expressed that there is not sufficient funding in current budgets to cover the cost of screening the very large number of patients that realistically will be required for precision medicine trials. The third concern was funding for biospecimen collection which should be facilitated and promoted in order to provide robust banks to be used as a resource for the identification of correlative markers and other research studies. Fourth, as noted above, it is challenging to obtain funding for correlative studies embedded in NCTN trials or using NCTN trial specimens. A pool of dedicated NCTN funding for correlative studies would be a tremendous advantage in leveraging the investment in clinical trials to make new discoveries about underlying mechanisms of cancer. Finally, concern was expressed that current budgets do not cover the extra costs incurred for participating in NCTN registration trials. Based on these concerns, the Working Group recommended that NCI pursue all possible avenues to increase funding for some or all of these purposes.

APPENDIX 1 – WORKING GROUP MEMBERS

Chair

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Executive Secretary
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APPENDIX 2 – SOURCE MATERIALS USED IN THE EVALUATION

Material provided by NCI

1. Overview of the NCTN Program
2. Number of active studies and total accrual by phase and grant year
3. List of trials activated March 2014 – October 2016
4. List of concepts and letters of intent approved March 2014 – October 2016
5. Intervention accrual distribution by:
    a. Disease site
    b. Study phase
    c. NCTN role (LAPS, NCORP sites, Rostered Members, Cancer Centers)
6. Cross-Group intervention accrual and screening accrual to precision medicine trials
7. Accrual efficiency data (actual versus projected accrual rate) for the 14 phase III trials activated after March 2014 and open for at least 12 months
8. Trial activation timelines for trials activated March 2014 – November 2016
9. IND status of NCTN trials
10. List of open NCTN licensing/registration trials
11. Examples of NCTN trials unlikely to be conducted by industry
12. List of NCTN-associated quality of life studies activated March 2014 – October 2016
13. List of non-NCTN NIH grants supporting translational studies embedded in NCTN trials or using biospecimens from NCTN trials
14. IROC and ITSA activities since March 2014

Material from the NCTN Groups

15. Accomplishment highlights 2014 – 2016 provided by each NCTN Group
16. Results of a December 2016 stakeholder survey concerning satisfaction with various aspects of the NCTN. *The survey was sent to Group key personnel and leadership, LAPS PIs, and NCORP PIs and administrators. From a total of 922 unique participants emailed, there were 307 respondents. The survey asked about NCTN structure, processes, achievements and areas needing improvement.*
17. Anonymized comments concerning NCTN strengths and weaknesses provided by the Group Chairs at the request of the Working Group

APPENDIX 3 – ABBREVIATIONS

ACS	American Cancer Society
ALCHEMIST	Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trials
Alliance	Alliance for Clinical Trials in Oncology
CCTG	Canadian Cancer Trials Group
CIRB	Central Institutional Review Board
COG	Children's Oncology Group
CTAC	Clinical Trials and Translational Research Advisory Committee
CTEP	Cancer Therapy Evaluation Program
CTSU	Cancer Trials Support Unit
DART	Dual Anti-CTLA-4 and Anti-PD-1 Blockade in Rare Tumors
DoD	Department of Defense
ECOG-ACRIN	Eastern Cooperative Oncology Group-American College of Radiology Imaging Network
EURAMOS	European and American Osteosarcoma Study Group
IND	Investigational New Drug
IROC	Imaging and Radiotherapy Oncology Core Services
IT	Information Technology
ITSA	Integrated Translational Science Award
LAPS	Lead Academic Participating Site(s)
LLS	Leukemia & Lymphoma Society
LOI	Letter of Intent
LUNG-MAP	Lung Cancer Master Protocol
MATCH	NCI Molecular Analysis for Therapy Choice
NCI	National Cancer Institute
NCORP	NCI Community Oncology Research Program
NCTN	NCI National Clinical Trials Network
NEE WG	NCI National Clinical Trials Network External Evaluation Working Group
NIH	National Institutes of Health
NRG	NCTN Group that represents the consolidation of the National Surgical Adjuvant Breast and Bowel Project, the Radiation Therapy Oncology Group, and the Gynecology Oncology Group
OPEN	Oncology Patient Enrollment Network
PCORI	Patient-Centered Outcomes Research Institute
RFA	Request for Application
RSS	Regulatory Support Services
SPORE	Specialized Programs of Research Excellence
SWOG	Southwest Oncology Group
TailoRx	Trial Assigning Individualized Options for Treatment (Rx)