

NCI National Clinical Trials Network
(NCTN)
Working Group
Final Report
July 2014



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EXECUTIVE SUMMARY

The NCI National Clinical Trials Network (NCTN) Working Group (WG) was charged with assessing the strength and balance of active NCTN clinical trials and NCI Community Oncology Research Program (NCORP) symptom management and health related quality of life (SxQOL) trials both within and across portfolios and recommending future strategic priorities and directions. Section I of this report summarizes findings and recommendations relevant to the first charge, while Section II summarizes discussions and recommendations relevant to the second charge.

In response to the first charge, the NCTN WG held four meetings from July 2012 to July 2013 to review the NCI's active phase 3 and large phase 2 (≥ 100 patient) therapeutic clinical trials, clinical imaging trials, and SxQOL trials. Over the course of the four meetings, portfolios evaluated by fourteen Scientific Steering Committees were assessed. Those assessments resulted in cross-portfolio comments and recommendations aimed at improving the overall portfolio, as well as comments and recommendations for each individual portfolio.

Cross-portfolio comments and recommendations were generally similar across the four meetings, and resulted in 11 cross-portfolio recommendations. Although the portfolio-specific comments and recommendations demonstrate that the portfolios are of differing quality and have different strengths and weaknesses, many common concerns emerged. These included emphasizing innovative, science driven trials; considering a reallocation of NCTN resources across diseases and clinical trial activities; enhancing coordinated strategic planning and collaboration; strengthening evaluation criteria; and optimizing Steering Committee processes. The portfolio-specific comments and recommendations often mirror the cross-portfolio recommendations but are more detailed and also address the particular strengths and weaknesses, the state of the science, and other features distinctive to each portfolio.

Before pursuing the second charge, NCI and the NCTN WG Chairs agreed that rather than recommending specific priorities and directions it would be more useful for the WG to recommend a process for setting priorities and directions within and across portfolios on an ongoing basis. To that end, four meetings were held from December 2013 to March 2014 through which a comprehensive process for trial prioritization was developed. The process has three components: prospective portfolio-specific priority setting, identifying trial categories generally considered either high or low priority and a cross-disease prioritization process to rank resource-intensive trials in priority order for funding, if NCTN resource constraints necessitate.

Two of these meetings were NCTN WG meetings while the other two were organized under the auspices of the CTAC in order to obtain additional input on the approaches under discussion. One of these meetings involved the CTAC Program Planning Working Group¹, the CTAC Strategic Planning Subcommittee², the NCTN WG Chairs and NCI staff and discussed all aspects of NCTN trial prioritization. The second meeting was convened to pilot a process for cross-disease prioritization by examining two large Scientific Steering Committee approved concepts that were currently on hold because of potential NCTN funding constraints. This meeting involved members of the CTAC Clinical Trials Prioritization Working Group³ and NCI staff.

¹ Members are listed at <http://deainfo.nci.nih.gov/advisory/ctac/workgroup/ProgramPlanning/Roster.pdf>

² Members are listed at <http://deainfo.nci.nih.gov/advisory/ctac/subcommittees/StrategicPlanning/Roster.pdf>

³ Members are listed at <http://deainfo.nci.nih.gov/advisory/ctac/workgroup/CTpriority/Roster.pdf>



Over the course of these meetings, the value of and process for a periodic strategic assessment of each trial portfolio (similar to the portfolio assessment conducted by the NCTN WG from July 2012 - July 2013) was discussed. Based on those discussions, the NCTN WG concluded that such an assessment would be a valuable complement to prospective priority setting and cross-disease prioritization and recommended that the NCI conduct at least one additional strategic portfolio assessment.

March 26, 2014 marked the final meeting of the NCTN WG. As detailed in this report, the NCTN WG has now addressed two elements of its initial charge. Moreover, the NCTN WG deliberations in addressing these elements illustrated the usefulness of convening an advisory body of external stakeholders, and the value of gathering strategic input from multiple different extramural perspectives, when developing processes for enhancing the NCI clinical trials enterprise. Going forward, NCI and CTAC will consider whether to convene one or more additional Working Groups to address the remaining elements of the NCTN WG's charge⁴) and provide oversight for implementation of the NCTN WG's cross- portfolio and portfolio-specific recommendations, as well as implementation of the NCTN WG recommended processes for prospective portfolio-specific priority setting and cross-disease prioritization.

⁴ NCTN WG Charge is listed at <http://deainfo.nci.nih.gov/advisory/ctac/workgroup/NCTN/fo.pdf>.



Section I

Assessment of the NCTN and NCORP Clinical Trials Portfolios

1.1 INTRODUCTION

Section I of this report summarizes findings and recommendations relevant to the first charge of the NCTN WG which was to assess the strength and balance of active clinical trials both within and across portfolios. In response to this charge, the NCTN WG held four meetings from July 2012 to July 2013 to review the NCI's active phase 3 and large phase 2 (≥ 100 patient) therapeutic clinical trials, clinical imaging trials, and symptom management and health related quality of life (SxQOL) trials. Over the course of the four meetings, portfolios evaluated by fourteen Scientific Steering Committees were assessed:

- July 11, 2012 – colorectal cancer (CRC) trials from the gastrointestinal (GI) portfolio assessed as a pilot
- December 16-17, 2012 – breast, leukemia, GI minus CRC trials, lymphoma, and genitourinary (GU)
- March 27-28, 2013 – myeloma, thoracic, brain (adult and pediatric), and pediatric (solid tumor and leukemia and lymphoma)
- July 1-2, 2013 – gynecologic, clinical imaging, SxQOL, and head and neck

Those assessments resulted in cross-portfolio comments and recommendations aimed at improving the overall portfolio as well as comments and recommendations for each individual portfolio.

Cross-portfolio comments and recommendations were generally similar across the four meetings, and resulted in 11 cross-portfolio recommendations, which are presented in **Section 1.2**. Although the portfolio-specific comments and recommendations (see Section 1.3) demonstrate that the portfolios are of differing quality and have different strengths and weaknesses, many common concerns emerged. These included emphasizing innovative, science driven trials; considering a reallocation of NCTN resources across diseases and clinical trial activities; enhancing coordinated strategic planning and collaboration; strengthening evaluation criteria; and optimizing Steering Committee processes.

In particular, the cross-portfolio comments and recommendations focused on how to advance cutting-edge science in the genomics era by improving the integration of genomics and biomarkers into study designs, as well as enhancing the NCI's ability to conduct trials with an emphasis on molecular characterization and biomarker tests. Such strategies were considered important to attract industry collaborators and distinguish NCI in the global research arena. Implementing this strategy will require adequate and strategically deployed funding, as well as strong collaboration among the Scientific Steering Committees, the NCTN Groups, the NCI Community Oncology Research Program (NCORP) Research Bases and the NCI.

Because there has been progress in implementing some of these recommendations since the assessments were completed in July, 2013, Section 1.2 also includes a summary of current and planned implementation activities. Many of the planned activities will be implemented through new processes developed by the NCTN WG for addressing strategic priorities and directions for NCTN and NCORP⁵ clinical trials (see Section II of this report). These processes include prospective portfolio-specific priority setting, cross-disease prioritization of resource-intensive phase 3 trials invoked as necessary in response to NCTN resource constraints and periodic strategic assessments of trial portfolios.

⁵ For simplicity, the term "NCORP clinical trials" is used in this document to refer to the NCORP SxQOL trials. NCORP may conduct other types of clinical trials that are not covered by this report.



Portfolio-specific comments and recommendations, which are presented in **Section 1.3**, often mirror the cross-portfolio recommendations but are more detailed and also address the particular strengths and weaknesses, the state of the science, and other features distinctive to each portfolio.

The process and methodology description (**Section 1.4**) outlines the activities, timeline, and evolution of the portfolio assessment process. The approach for developing recommendations, the process for rating trials in each portfolio and the purpose and meaning of those ratings are also discussed in Section 1.4.



1.2 CROSS-PORTFOLIO RECOMMENDATIONS

Eleven cross-portfolio recommendations aimed at improving the portfolios – and directed jointly to the NCTN Groups, the NCORP Research Bases, the Scientific Steering Committees and the NCI – emerged during the assessment. The recommendations fell into five major categories:

- Emphasize innovative science driven trials
- Consider reallocation of NCTN resources
- Enhance coordinated strategic planning and collaboration
- Strengthen evaluation criteria
- Optimize Steering Committee processes

The cross-portfolio recommendations that resulted from the December 2012 meeting were generally re-affirmed at the subsequent meetings in March and July 2013. For recommendations which did not specifically arise in either of the 2013 meetings, there are two potential explanations. First, certain recommendations may not have been as relevant for the portfolios discussed. Secondly, it is possible that the WG members felt less urgency to reiterate their support for recommendations raised in earlier meetings. No additional cross-portfolio recommendations arose from the March or July 2013 discussions. However, in preparing this final report one of the original ten recommendations was divided into two recommendations without a change in substance. The recommendations are not listed here in order of importance but rather grouped into the relevant categories.

Emphasize Innovative Science Driven Trials

1. NCI, NCTN Groups, NCORP Research Bases, and the Scientific Steering Committees should work together to achieve an appropriate balance of innovative, randomized phase 2 trials and larger more resource intensive phase 3 trials in each portfolio.

Implementation Status/Plans

- Proactively communicated recommendation to the NCTN Groups, the NCORP Research Bases and the Scientific Steering Committees
 - Balance to be emphasized when establishing strategic priorities for each portfolio
 - Performance to be monitored through periodic strategic assessment of trial portfolios
2. NCTN Groups, NCORP Research Bases and the Scientific Steering Committees should emphasize biology-driven (e.g., molecularly-driven, pathway-driven) trials that advance the science by incorporating genomics, biomarker tests and correlative science into study designs.

Implementation Status/Plans

- Proactively communicated recommendation to the NCTN Groups, the NCORP Research Bases and the Scientific Steering Committees
- Biology driven trials to be emphasized when establishing strategic priorities for each portfolio
- Performance to be monitored through periodic strategic assessment of trial portfolios
- Scientific impact/contribution to be one of the primary criteria for new cross-disease prioritization process



Consider Reallocation of NCTN Resources

3. NCI, working with the extramural community, should conduct an analysis of resource allocation across diseases, taking into account current survival rates and likely cost/benefit from additional advances.

Implementation Status/Plans

- Extramural discussions did not support upfront budget allocation to each disease, concluding allocation should be driven by the science
 - Cross-disease prioritization of resource-intensive trials will consider current resource allocation
4. To empower innovative, biology-driven trials, additional NCI funding should be provided for correlative science studies, biomarker validation, tissue collection, and the development of molecular classification algorithms.

Implementation Status/Plans

- NCI funds are set aside annually for performing integral and integrated biomarker, imaging and quality of life studies in association with NCTN or NCORP clinical trials
- NCI is pursuing creative partnerships with the Foundation for the NIH, other philanthropic organizations, and industry partners to fund integral, integrated and correlative studies in association with NCTN or NCORP trials
- The R21 grant mechanism, which is intended to encourage exploratory/developmental research by providing support for early and conceptual stages of project development, is an approach for funding innovative correlative studies in association with NCTN or NCORP trials

Enhance Coordinated Strategic Planning and Collaboration

5. Scientific Steering Committees should increase their involvement in strategic planning and guidance for future trials in collaboration with the NCTN Groups, the NCORP Research Bases and NCI.

Implementation Status/Plans

- Clinical Trials Planning Meetings currently provide one avenue for such involvement
 - New process for setting portfolio-specific strategic priorities will substantially increase involvement
6. Greater emphasis should be placed on sharing strategic and tactical best practices across portfolios in terms of trial design, accrual, preliminary data requirements, etc.

Implementation Status/Plans

- Periodic strategic assessment of trial portfolios will provide a regular venue for sharing best practices
7. NCI, NCTN Groups, NCORP Research Bases and the Scientific Steering Committees should continue to pursue collaborations with international and industry partners and address barriers to these collaborations.

Implementation Status/Plans

- Public-private partnerships (e.g., Lung Cancer Master Protocol) provide a novel template for such collaborations



Strengthen Evaluation Criteria

8. More attention should be paid to accrual challenges in proposing and approving trial concepts, balancing the importance of the clinical question with the perceived difficulty of accrual.

Implementation Status/Plans

- Proactively communicated recommendation to the NCTN Groups, the NCORP Research Bases and the Scientific Steering Committees
 - Emphasizing importance of accrual challenges in Scientific Steering Committee evaluations
 - NCI closely monitoring accrual performance
9. More consideration should be given to competing international and industry trials in proposing and approving trial concepts.

Implementation Status/Plans

- Proactively communicated recommendation to the NCTN Groups, the NCORP Research Bases and the Scientific Steering Committees
 - Emphasizing importance of competing trials in Scientific Steering Committee evaluations
 - Competing trials important criterion for new cross-disease prioritization process
10. Scientific Steering Committees should develop standardized guidelines for the level and types of preliminary data required for trial concepts.

Implementation Status/Plans

- NCTN Groups, NCORP Research Bases, Scientific Steering Committees and NCI plan to work together to develop portfolio-specific guidelines for preliminary data requirements
- Implementation to be monitored through periodic strategic assessment of trial portfolios

Optimize Steering Committee Processes

11. Scientific Steering Committees should optimize their use of Task Forces, Working Groups and Clinical Trial Planning Meetings.

Implementation Status/Plans

- Proactively communicated recommendation to the NCTN Groups, the NCORP Research Bases and the Scientific Steering Committees
- Implementation to be monitored through periodic strategic assessment of trial portfolios



1.3 PORTFOLIO SPECIFIC FINDINGS AND RECOMMENDATIONS

The results of the NCTN WG discussions of the overall portfolio evaluation process are summarized below.

DECEMBER 2012

Breast Cancer Portfolio

Portfolio

Strengths

- Portfolio is strong and addresses many key questions
- Balances systemic and local-regional trials
- Highly suitable for the NCTN Program
- Successful in conducting practice-changing trials

Recommendations to Address NCTN WG Concerns

- Develop smaller, more molecularly driven earlier phase trials to balance preponderance of large adjuvant studies offering only incremental clinical benefit
- Place more emphasis on studies to limit toxicity, improve QOL, assess survivorship/secondary cancers, etc. given the high survival rate in this disease
- Focus more on metastatic, DCIS, and inflammatory breast cancers
- Bank biospecimens from large adjuvant trials for future R01 correlative and The Cancer Genome Atlas (TCGA) studies and develop a plan for use of banked samples
- Focus more attention on feasibility issues, i.e. accrual and the practicality of the randomization scheme
- Give more consideration to community standards of care in trial design

Scientific Steering Committee Process

Comments/Recommendations

- Be more strategic and not just focus on details of individual studies
 - Make more use of TFs and/or ad hoc WGs for early vetting, preventing development of redundant protocols, and improving communication between the Breast Cancer Steering Committee (BCSC) and the NCTN Groups
 - BCSC and the NCTN Groups should jointly develop guidance on the types of trials that are likely to be acceptable to minimize wasted effort
 - Consider whether to approve trials competing with ongoing trials outside the NCTN Program
-



Gastrointestinal (GI) Portfolio Minus Colorectal

Portfolio

Strengths

- Trials moving in the right direction by increasingly addressing clinically important questions
- Trials with existing agents, while incremental, could be practice-changing
- Diverse portfolio with an appropriate focus on rare diseases
- Trials appropriate for the NCTN Program and address questions industry is unlikely to support (e.g. correlative science, QOL)

Recommendations to Address NCTN WG Concerns

- Develop more biology-based, genomics-based, and pathway-directed trials even in rare cancers including molecular classification for case or treatment selection
 - Many trials seem empirical and not hypothesis driven
 - Few targeted therapy trials and existing targeted trials pose accrual challenges and concerns such as payment for screening
- Incorporate more imaging, QOL and surgery questions into trials.
- Work more with industry so good questions requiring industry partners can be pursued
- Increase foreign recruitment to help ease accrual problems.
- Try to develop a paradigm for predicting which agents might work in the adjuvant setting even if they failed in the metastatic setting

Scientific Steering Committee Process

Comments/Recommendations

- The Gastrointestinal Steering Committee (GISC) has a generally strong process; strengths include concept pre-review, intergroup and international collaboration, organization and efficiency
- GISC use of WGs and especially TFs has significantly improved protocols
- Recommend strengthening process and criteria for assessing accrual feasibility
- Guidelines on the level of preliminary data required for approval should be developed



Genitourinary (GU) Portfolio

Portfolio

Strength

- Trials address questions that industry would not

Concern

- Many trials viewed as testing outdated approaches and regimens given the rapidly changing landscape and the standard options currently available in GU cancers

Recommendations to Address NCTN WG Concerns

- Focus on developing innovative, molecularly-driven trials asking scientific questions that will advance the field and incorporate molecular correlates and biomarkers
- Develop more multidisciplinary studies (e.g., combine surgery and radiation, drug combinations)
- Increase inclusion of QOL studies and use of patient reported outcomes across the portfolio, and assessment of the impact of co-morbidities and performance status in bladder cancer
- Consider development of radiation technology assessment trials and technology comparative assessment studies
- Address accrual problems, including legacy studies competing for patients with newer more exciting studies
- Consider concentrating investment in diseases with poorer outcomes as opposed to prostate (with excellent outcome in most patients) or in trials to better manage early stage and low grade prostate cancer

Scientific Steering Committee Process

Comments/Recommendations

- Interact more closely with the NCTN Groups to strategically shape the future trial portfolio
- Consider balance between large phase 3 prostate trials and other diseases and trial types when making approval decisions
- Avoid approving trials that compete for the same patient populations
- Trials were disapproved for appropriate reasons
- Consider forming one or more TFs to look at pathway modulation or biomarkers for advanced disease
- More actively promote implementation of recommendations from CTPM meetings



Leukemia Portfolio

Portfolio

Strengths

- Strong portfolio of innovative, biologically-based, scientifically and clinically important trials
 - Chronic Lymphocytic Leukemia (CLL) trials in older adults are noted strength
 - Excellent capture of older AML patients in national trial
- Good breadth of disease coverage
- Strong tissue banking that will facilitate post-hoc correlative studies

Recommendations to Address NCTN WG Concerns

- Emphasize molecularly-driven and pathway-specific trials, especially for Acute Lymphoblastic Leukemia (ALL) and Acute Myeloid Leukemia (AML)
- Increase focus on use of biomarkers, including pre-trial molecular profiling and post-hoc correlative studies
 - Create infrastructure to build molecular classification algorithms for patient stratification
 - Create mechanism for funding collection and screening of multiple bone marrow samples to identify eligible subjects as well as a centralized process for screening tests
- Focus less on transplants and more on targeted agents, relapsed disease, and the elderly
- Improve accrual so trials do not take so long to complete
 - Develop a plan for terminating older trials that are accruing slowly

Scientific Steering Committee Process

Comments/Recommendations

- Functions well to refine and develop trial ideas
 - Thinks in strategic terms rather than trial-by-trial
 - Modifies and improves concepts as new information becomes available
 - Trials approved by Scientific Steering Committee stronger than pre-Scientific Steering Committee studies
- Fosters strong intergroup collaboration



Lymphoma Portfolio

Portfolio

Strength

- Appropriate focus on randomized phase 2 trials; phase 3 studies may have been premature

Concern

- Trials having low impact in lymphoma because the best new agents are being tested in European and industry trials not through the NCTN Groups

Recommendations to Address NCTN WG Concerns

- Create a niche in advancing the science by improving incorporation of innovative correlative and translational science into trial concepts including use of integral and integrated biomarkers and molecular characterization of patients
 - Greatest potential to distinguish trials from industry and Europe
- Pursue collaborations with Europeans, rather than duplicating European studies
- Design phase 2 trials to advance scientific understanding, resolve questions and inform design of phase 3 trials; do not conduct phase 2 trials that are essentially underpowered phase 3 trials
- Develop approach for addressing accrual issues, including competition with European trials and the challenges presented by parsing lymphoma into small patient populations based on molecular distinctions
- Assess why trials tend to be slow to activate and complete
- Avoid trials with long follow-up times as that poses funding issues
- Analyze why it has been difficult to develop lymphoma phase 3 trials through the NCTN Group system

Scientific Steering Committee Process

Comments/Recommendations

- Several strengths identified including working on strategic planning, face-to-face meetings with the NCTN Groups to work out details of proposed concepts, attempts not to duplicate what is being done elsewhere, appropriate decisions on the disapproved concepts, and standardizing clinical trial elements (e.g. eligibility criteria for certain diseases)
- During review, consider whether concepts for randomized phase 2 trials are designed to inform or lead to phase 3 trials
- When evaluating concepts, consider their positioning relative to European and industry trials

Myeloma Portfolio

Portfolio

Strengths

- Trials based on good biology and asking important scientific questions
- Portfolio covers all types of myeloma, including standard and high risk, and first and later relapses
- Portfolio investigates questions industry would not, especially examining how best to implement new drugs in practice – for example, the lenalidomide maintenance therapy duration study
- Good focus on QOL
- Important imaging components in several studies
- Move to oral proteasome inhibitors

Recommendations to Address NCTN WG Concerns

- Consider appropriate niche for NCTN myeloma research, particularly whether to focus on questions not being addressed by industry or to work more closely with industry to conduct research on novel agents
- Consider whether the current focus on proteasome inhibitors should be broadened
- Explore opportunities to address transplant questions, which may ultimately have more impact on QOL outcomes than agents and will not be pursued by industry; consider building on NCI/NHLBI collaborations for transplant-related studies
- Develop future studies related to stem cells and the tumor microenvironment
- Explore ways to better measure QOL
- Pursue studies examining the diversity of biology and outcomes as a function of racial and ethnic demographics
- Consider collaboration with Europeans in future studies, particularly to address accrual challenges

Scientific Steering Committee Process

Comments/Recommendations

- Myeloma Steering Committee (MYSC) has done a good job of working with the NCTN Groups to revise protocols and thinking strategically about approvals and disapprovals
- Accrual WG viewed as an excellent initiative
- Recommend conducting a formal evaluation of whether the Accrual WG has had a positive effect on accrual performance



Thoracic Malignancies Portfolio

Portfolio

Strengths

- Strength of concepts submitted to the Thoracic Malignancy Steering Committee (TMSC) has improved over time
- Excellent job carving out NCTN niche and not directly competing with industry
- Recent trials incorporate local treatment modality approaches and biomarkers, in addition to testing new agents
- Master screening protocols linked with testing of multiple therapies viewed as important advance, including the collaboration with TCGA to sequence specimens from the ALCHEMIST screening protocol

Recommendations to Address NCTN WG Concerns

- Improve the utility of master screening protocols
 - Find ways to accrue a larger proportion of screened patients to NCTN trials
 - Form closer collaborations with industry so that screened patients ineligible for NCTN studies can be referred to industry protocols
 - Ensure that screened patients are representative of national population

Scientific Steering Committee Process

Comments/Recommendations

- TMSC has placed a priority on not approving new trials that compete for accrual with ongoing legacy studies
- TMSC has done a good job as a central clearinghouse for NCTN Group concepts as there was not a strong intergroup process prior to the formation of TMSC
- The Working Group on Master Protocols viewed as a good initiative
- Disapproved trials were rejected for good reasons, mainly lack of adequate preliminary data
- TMSC should consider ways to examine and mitigate barriers to accrual, possibly by implementing an Accrual Working Group as in myeloma



Brain Malignancies Portfolio

Portfolio

Strengths

- Pediatric brain cancer generally viewed as a strong portfolio of trials

Recommendations to Address NCTN WG Concerns

- Broaden scope of adult brain portfolio beyond bevacizumab and try to develop some late phase trials
- Focus on developing more biology-based, genomics-based, and pathway-directed trials involving biomarkers
- Integrate genomics and correlative science into future protocols whenever possible perhaps through collaboration with the adult brain Specialized Programs of Research Excellence (SPOREs)
- More consideration should be given as to whether studies should be designed as phase 2 or phase 3
- Develop a strategy for obtaining novel agents, since many drugs are held by industry and not available to the CTEP
- Explore combination therapies as single agents are often not optimally effective

Scientific Steering Committee Process

Comments/Recommendations to Address NCTN WG Concerns

- Brain Malignancy Steering Committee (BMSC) should strive for better collaboration with NCTN Groups including strategic planning for the disease area
- BMSC should consider reviewing all phase 2 protocols for adult brain cancer, as they do for pediatrics



Pediatric Portfolio

Portfolio

Strengths

- Current portfolio represents a good balance between focusing on improving survival toward 100% and reducing toxicities
- Strategy of focusing future studies on reducing toxicities, improving quality of life, and addressing survivorship issues

Recommendations to Address NCTN WG Concerns

- Focus more on targeted agents
 - Need strategy for assessing which targets are druggable perhaps drawing on the NCI TARGET (Therapeutically Applicable Research to Generate Effective Treatments) Initiative to identify molecular targets and prognostic markers for pediatric cancers
- Search for new approaches to engage industry in pediatric cancers
- Consider extending the age range of eligibility for pediatric trials to reach more of the young adult population
- Seek more collaboration with adult oncology, especially in hematological malignancies

Scientific Steering Committee Process

Comments and Recommendations

- The new Pediatric Leukemia and Lymphoma Steering Committee (PLLSC) process of conducting “pre-reviews” of Children’s Oncology Group (COG) submitted concepts was viewed as a positive development
- Scientific Steering Committee revisions to submitted protocols have been constructive
- Disapproved trials were disapproved for appropriate reasons

Gynecologic Cancer Portfolio

Portfolio

Strengths

- Recent increase in randomized phase 2 and phase 3 trials over single arm phase 2 trials
- Strong international collaborations
- Generally strong accrual record

Recommendations to Address NCTN WG Concerns

- Achieve better balance between innovative, science-driven trials and incremental/confirmatory trials
- Focus on translational science with clear endpoints and goals including greater collaboration with SPOREs and other translational investigators
- Pursue more systematic design of trials based on past positive or negative results
- For ovarian trials, include endpoints other than PFS and expand beyond the current focus on bevacizumab
- In the cervical portfolio, focus more on detection, prevention and radiation therapy trials
- Gynecologic Oncology Group (GOG) and Gynecologic Cancer Steering Committee (GCSC) along with the NCI should work together more closely in developing future strategic directions

Scientific Steering Committee Process

Comments/Recommendations to Address NCTN WG Concerns

- Good progress in working with GOG and integrating GCSC, TF, and GOG processes for concept review
- CTPMs have been used effectively but could be improved by including more translational researchers and focusing future meetings on translational science
- Interact with the pediatric Scientific Steering Committees to share best practices on handling portfolios dominated by a single submitting group



Clinical Imaging Portfolio

Portfolio

Strengths

- Successfully addresses tumor heterogeneity
- Approved studies have good accrual feasibility

Recommendations to Address NCTN WG Concerns

- Enhance use of more clinically meaningful endpoints
- Emphasize trials that aim for more than incremental improvements
- Identify opportunities for larger, more innovative imaging studies

Scientific Steering Committee Process

Comments/Recommendations to Address NCTN WG Concerns

- Clinical Imaging Steering Committee (CISC) provided good feedback that improved trials
- CISC effectively avoids duplicative review by only reviewing trials where imaging is the primary focus
- CISC provides additional value by serving as a pool of imaging experts for Scientific Steering Committees in review of trials with secondary imaging components
- CISC should convene periodic workshops involving imagers and clinical trialists with the goal of enhancing integration of imaging components into disease-specific clinical trials
- CISC should encourage and facilitate follow through on trial ideas emerging from future CTPMs



Symptom Management and Health Related Quality of Life (SxQOL) Portfolio

Portfolio

Strengths

- Addresses wide variety of symptoms across many disease sites
- Good accrual record
- Science uniquely suited to the NCTN because would not be done without public funding

Recommendations to Address NCTN WG Concerns

- Emphasize trials of new interventions in order to achieve a better balance with trials that disprove or confirm current interventions
- Strengthen the basic science and preclinical foundation for trial
 - Develop a strategy for obtaining more NCI support for basic research and generation of preclinical data in this area
 - Collaborate with symptom management scientists working in other fields (e.g. neurology, rheumatology) to leverage synergies
- Conduct fewer, but more in depth, trials with the following characteristics:
 - Based on strong biological evidence
 - Exploring innovative agents
 - Comparing interventions against one another rather than placebo
 - Employing multi-agent regimens
- Pursue more systematic design of trials based on past positive or negative results
- NCORP Research Bases, the NCI and the SxQOL Steering Committee SC should collaborate in developing strategic directions which could include:
 - Developing science based RFAs designed to fund the strongest study in each symptom
 - Prioritizing those symptoms with the best potential for progress and concentrating trials on those symptoms
- NCORP Research Bases and the SxQOL SC should collaborate in developing and implementing standard data definitions, endpoints, etc. so trials can more easily be compared
- Collaborate with other National Institutes of Health (NIH) institutes (e.g. neurology, rheumatology)
 - Coordinate NIH funding more effectively for basic science and preclinical studies
 - Engage pharmaceutical companies in discussing the potential of symptom management agents



- Develop more interaction between clinical and symptom management teams in developing symptom management studies
- Develop a process to better ensure agent availability for proposed concepts

Scientific Steering Committee Process

Comments/Recommendations to Address NCTN WG Concerns

- Effective in selectively approving concepts, managing the portfolio and advising on study design
- Effective forum for sharing ideas, trial designs, etc.
- Consider adding basic and preclinical symptom scientist members
- Actively engage Disease-Specific Scientific Steering Committees to encourage inclusion of SxQOL studies in appropriate trials
- Focus future CTPM on translational science and biological mechanisms



Head and Neck Cancer Portfolio

Portfolio

Strengths

- Strong portfolio in several respects
 - Potentially practice-changing trials
 - Endpoints aggressive and seek major increases in benefit instead of incremental progress
 - Effective incorporation of QOL endpoints
 - Testing low toxicity regimens
 - Incorporating biology despite limitations of therapeutic options
- Successfully employs Human Papillomavirus (HPV) and Epstein-Barr Virus (EBV) biomarker stratification for understanding subpopulations
- Good collection of tissue samples given access issues
- Effective pursuit of international collaborations
- Uniquely suited to the NCTN Program as trials would not have been done by industry

Recommendations to Address NCTN WG Concerns

- Improve incorporation of biological and translational advances such as next-generation sequencing and understanding of disease mechanisms into trial designs
- Place more emphasis on designing strong translational science studies to make optimal use of collected tissues
- Pursue more interaction with SPOREs to address the lack of translational science
- Pursue more interaction with investigators performing single arm phase 2 trials outside the NCTN Program to identify emerging opportunities

Scientific Steering Committee Process

Comments/Recommendations to Address NCTN WG Concerns

- Head and Neck Steering Committee (HNSC) has achieved appropriate balance of review and collaborative development of concepts
- May serve as a model for how other Scientific Steering Committees should operate



1.4 PROCESS AND METHODOLOGY

The NCTN WG portfolio assessment process and methodology evolved over the course of the four meetings held from July 2012 to July 2013. Over time, the NCTN WG developed more effective ways to review, discuss and rate trials, and develop strategic recommendations to improve portfolios.

Meeting Timeline

Pilot Meeting: In July 2012, the NCTN WG piloted the assessment process utilizing the CRC clinical trials portfolio and determined that review of individual trials within a portfolio is appropriate and feasible. The WG concluded that presentations of clinical trial portfolios and future strategies by NCI Medical Officers from the CTEP or the Division of Cancer Prevention (DCP) and the Scientific Steering Committee Chairs is valuable to contextualize trials and understand the basis for Steering Committee decisions to approve or reject individual trial concepts and shape portfolios.

At this meeting, the WG refined the trial evaluation criteria and suggested improvements to the evaluation process. These included the following: assigning WG members to portfolio-specific Subgroups that would analyze a given portfolio in depth prior to a meeting; providing summary information on major ongoing trials beyond the NCTN (e.g., industry, international) for each portfolio; and assigning each trial an overall rating, in addition to rating the trials on the individual evaluation criteria.

December 2012, March 2013, and July 2013 Meetings: 14 trial portfolios were assessed at the three meetings following the pilot meeting: breast, GI except CRC, GU, leukemia and lymphoma in December 2012; myeloma, thoracic, brain (adult and pediatric) and pediatric (solid tumors and leukemia and lymphoma) in March 2013; and gynecologic, clinical imaging, SxQOL, and head and neck in July 2013. A summary of NCTN WG activities prior to, during and after these meetings is provided below, with changes over time highlighted.

Meeting Process

Review Materials: In advance of each meeting, all WG members were provided trial summaries, which included schema, eligibility criteria, primary and secondary endpoints, stratification and sample size, adjunct studies and Scientific Steering Committee deliberation summaries, as well as information on the dates of concept review and trial activation, accrual status, and potential population benefit.

Subgroups: For each meeting, NCTN WG members were divided into portfolio-specific Subgroups, led by a Subgroup Chair. Subgroups were tasked with conducting an in depth analysis of their assigned trial portfolio, including all Scientific Steering Committee approved trials open to accrual, approved concepts not yet activated, and (in the December 2012 meeting, but abandoned in later meetings) selected phase 3 trials open to accrual but approved prior to establishing the Scientific Steering Committee. While the analysis focused on approved concepts, disapproved concepts were also examined.

Subgroup Pre-Meeting Activities: Subgroups conducted an in depth review of the trial information provided by NCI, discussed the trials with the NCI Medical Officer(s) and Scientific Steering Committee Chair(s), and assigned members to lead the discussion on concepts sufficiently complex or controversial as likely to warrant substantial discussion at a WG meeting. The Subgroups also identified issues with the portfolio to raise for discussion and developed broad preliminary conclusions and recommendations to be discussed with the full WG.



Activities during an NCTN WG Meeting:

- 1. Presentation of Trial Portfolio and Strategy by Scientific Steering Committee leadership and the NCI Medical Officer**
The NCI Medical Officer presented background information and issues for clinical trials and the state of the science in the disease/research area. The Scientific Steering Committee Chair(s) presented a summary of Scientific Steering Committee approved concepts, and complex or controversial aspects of select disapproved concepts. The presenters then discussed their future strategy for the portfolio.
- 2. Initial Open Discussion**
The WG asked questions and engaged in discussion with the NCI Medical Officer and Scientific Steering Committee Chair(s).
- 3. Closed WG Discussion** (*Scientific Steering Committee Chair(s) and NCI Medical Officer excused*)
WG members rated each trial on five criteria and gave each trial an overall rating using an electronic ballot (see p. 28). The WG then engaged in closed discussion, reviewed the trial ratings and their consistency with WG comments, and prepared conclusions and recommendations.
- 4. Final Open WG Discussion** (*Scientific Steering Committee Chair(s) and NCI Medical Officer rejoin discussion*)
Trial ratings, conclusions and recommendations were shared with the NCI Medical Officer(s) and Scientific Steering Committee Chair(s), and all participants continued to dialogue and refine final feedback on the portfolio.

Post-Meeting Activities: Written summary reports of NCTN WG findings were prepared following each meeting, reviewed and refined, and shared following and between meetings. Post-meeting activities also included:

- 1. Development of Cross-Portfolio Recommendations**
Ten cross-portfolio recommendations were first formulated after the NCTN WG December 2012 meeting. After each subsequent meeting, comments on the applicability of the recommendations to the newly evaluated trial portfolios were added. No additional overarching recommendations emerged in the March 2013 and July 2013 meetings. In preparing this final report one of the original ten recommendations was divided into two recommendations without a change in substance.
- 2. Presentations of NCTN WG Meeting Summary Findings to the Clinical Trials and Translational Research Advisory Committee**
The cross-portfolio and portfolio-specific recommendations were presented by the NCTN WG Chair(s) and discussed at CTAC meetings in March and November, 2013.
- 3. Discussions on NCTN WG Process**
During the March 2013 meeting, the WG discussed the December 2012 Meeting Summary Notes and determined that they concisely and accurately reflected the major conclusions and topics of discussion from the December 2012 meeting. Feedback during this session informed future meetings.

During the July 2013 meeting, the WG discussed the interpretation of trial rating results, whether and in what form the trial ratings should be shared outside the NCTN WG, the process for communicating the NCTN results to portfolio-specific stakeholders, and agenda items for future NCTN WG meetings. The WG concluded that the trial ratings reasonably reflect the relative strengths of the portfolios compared



to one another, but emphasized that trial ratings should be viewed as a tool for better understanding portfolios, not a grade or a score for each trial, as the purpose was not to re-litigate trials. Moreover, in communicating results of the WG process to portfolio-specific stakeholders, the WG recommended anonymizing the trial ratings and emphasizing the comments and recommendations not the trial ratings. The WG also wanted the WG process and methodology to be shared with stakeholders, and for it to be clear that recommendations for portfolio improvement are directed jointly to the NCTN Groups, the Scientific Steering Committees and the NCI.

4. Stakeholder Calls to Review Findings

Fourteen stakeholder calls, one for each NCTN portfolio evaluated, were conducted between August and December of 2013 to communicate conclusions concerning the strength and balance of each portfolio and recommendations for improvement. The calls were designed to initiate a dialogue with stakeholders about the WG's assessment of their portfolios and next steps for the portfolio recommendations. Stakeholders invited included: NCTN WG Chairs, Subgroup Chairs and members, NCTN Group Chairs and NCTN Group Disease Committee Chairs, NCORP Research Base Principal Investigators (for SxQOL portfolio), Scientific Steering Committee Co-Chairs, Task Force Chairs, and leadership, medical officers and other staff from the NCI's Division of Cancer Treatment and Diagnosis (DCTD), DCP, and the Coordinating Center for Clinical Trials (CCCT).

Recommendations

The purpose of evaluating current trials was to engage the NCTN WG in thinking strategically about each portfolio, identifying strengths and potential gaps or deficiencies, and recommending potential future improvements. The portfolio-specific Subgroups generated initial recommendations during pre-meeting conference call discussions, which were presented to the WG at the face-to-face meeting, modified based on WG discussions, and refined after the meeting into a final set. The recommendations were primarily derived from the discussion, rather than from the ratings of individual trials.

Trial Ratings

The trial rating process, criteria, and scoring rubric were developed at the July 2012 meeting and further refined over time. The six criteria used to rate trials in the initial meeting were reduced to five for subsequent meetings (see table below). The wording and definitions of the criteria were also clarified and public health impact was eliminated as a separate criterion. However, public health impact continued to be assessed in discussions about clinical importance and study design, as well as in broader discussions about portfolio strength.

The five criteria used to rate trials at the subsequent meetings (December 2012, March 2013 and July 2013) were scientific contribution, clinical importance, feasibility, unique suitability for the NCTN program, and manageable cost/resource burden. However, confusion on the meaning of manageable cost/resource burden made ratings unreliable; that category was therefore removed from the data reported.

NCTN WG Rating Criteria	
July 2012 Pilot Meeting	December 2012, March 2013, July 2013 Meetings
Scientific/clinical importance of study question	Scientific Contribution
Strength of trial design	Clinical Importance
Accrual rate relative to expectations	Feasibility
Resource requirements	Manageable cost/resource burden
Appropriateness for conduct by the NCTN Program	Appropriateness for NCTN Program
Public Health Impact	



Each WG member rated all trials high, medium or low for each of the five criteria and assigned each trial an overall rating. The scoring rubric for the five criteria remained the same across all meetings, but the overall scoring rubric changed from a three- to a five-point scale to promote greater spread in overall ratings after the December 2012 meeting results revealed heavy clustering of overall ratings toward a medium score.

NCTN WG Scoring Rubric for the Five Criteria and Overall Rating		
Scoring Rubric	December 2012 Meeting	March and July 2013 Meetings
Five Criteria <i>(Stayed the same)</i>	<ul style="list-style-type: none"> • High • Medium • Low 	<ul style="list-style-type: none"> • High • Medium • Low
Overall Rating <i>(Changed)</i>	<ul style="list-style-type: none"> • High • Medium • Low 	<ul style="list-style-type: none"> • 1 – Outstanding • 2 – Excellent • 3 – Good • 4 – Fair • 5 – Poor

Rating the trials was a tool designed to focus WG members’ attention on the specifics of each trial. The ratings were determined by expert judgment using the factors listed below as a guide and not according to a rigorous, validated set of standards. Moreover, the manner in which the ratings were applied may have changed as the WG process evolved.

Factors Used to Rate the Four Criteria	
Feasibility	<ul style="list-style-type: none"> • Accrual difficulty • Time and cost to implement at sites
Clinical Importance	<ul style="list-style-type: none"> • Importance of study question relative to state of the science in the disease • Benefit per patient and for population (e.g. life years saved) • Benefit in light of disease context
Scientific Contribution	<ul style="list-style-type: none"> • Tests important scientific or clinical proof of principle question • Importance of integral or integrated correlative study questions
Unique Suitability for the NCTN Program	<ul style="list-style-type: none"> • Understudied/rare diseases or understudied populations • Radiotherapy/surgery/imaging techniques • Combination trials • Therapy optimization trials (e.g., alternative regimens) • Unlikely to be performed by industry • Provides important tissue or data resources for public use

Because of these considerations, individual trials should not be compared to one another based on the NCTN WG trial ratings. Rather, the ratings provide an indication of the relative overall quality of a given trial portfolio compared to the entire NCTN portfolio and also the relative rating of the trials in a portfolio on each criterion. Lastly, the ratings did/will not result in any action or decision on current trials.

Process Limitation

The major limitation to the NCTN WG process and methodology is that not all active trials in each portfolio were analyzed. After the December 2012 meeting, it was decided by NCI to only include those concepts approved by a Scientific Steering Committee in the NCTN WG evaluation. Because some Scientific Steering Committees have only recently been established, in some portfolios there may be a substantial fraction of the active trials that were not included in the WG evaluation. Therefore, the validity of any conclusions about those particular portfolios may be in question because they are not based on the full portfolio.



Section II

Approaches for Prioritization and Strategic Assessment of the NCTN and NCORP Clinical Trials Portfolios



2.1 INTRODUCTION

Section II of this report summarizes discussions and recommendations relevant to the second charge of the NCTN WG, which was to recommend strategic priorities and directions for NCTN and NCORP clinical trials. Before pursuing this charge, NCI and the NCTN WG Chairs agreed that rather than recommending specific priorities and directions it would be more useful for the WG to recommend a process for setting priorities and directions within and across diseases⁶ on an ongoing basis. To that end, the NCTN WG held an initial meeting on December 19, 2013 to discuss potential approaches for priority setting within and across diseases. Members of the CTAC Strategic Planning Subcommittee⁷ were invited by NCI and the NCTN WG Chairs to join in the December 19 discussion.

The results of this initial meeting were then discussed with the CTAC Chair, the CTAC Program Planning Working Group⁸, the CTAC Strategic Planning Subcommittee, the NCTN WG Chairs and NCI staff on February 26, 2014 in order to obtain additional input on the approaches under discussion prior to the NCTN WG meeting on March 26, 2014. During the February 26 meeting, participants concurred with NCI and the NCTN WG Chairs that it would be useful to pilot a process for cross-disease prioritization by examining two large Scientific Steering Committee approved concepts that were currently on hold because of potential funding constraints. That pilot process, which was conducted by the CTAC Clinical Trials Prioritization Working Group⁹ on March 11, 2014, provided valuable input to the deliberations of the NCTN WG at the March 26 meeting. In addition, the NCTN WG recommends that a periodic strategic assessment of each disease-specific trial portfolio, similar to the portfolio assessment conducted by the NCTN WG from July 2012 - July 2013, be conducted as a complement to prospective priority setting and cross-disease prioritization.

The combined results of the deliberations at these four meetings are presented in Section II of the NCTN WG Report. **Section 2.2** describes and recommends a comprehensive process for NCTN clinical trial prioritization which has three components:

- Prospective disease-specific priority setting (**Section 2.2A**)
- Trial categories generally considered either high or low priority (**Section 2.2B**)
- Cross-disease prioritization for resource intensive trials if necessitated by resource constraints (**Section 2.2C**)

Section 2.3 describes and recommends a process for a periodic strategic assessment of each disease-specific trial portfolio as a complement to the prioritization process.

⁶ For convenience in language, Section II of this report uses the term “disease” and “disease-specific” to refer not only to trials in particular organ sites, but also to SxQOL and Imaging trials.

⁷ Members are listed at <http://deainfo.nci.nih.gov/advisory/ctac/subcommittees/StrategicPlanning/Roster.pdf>.

⁸ Members are listed at <http://deainfo.nci.nih.gov/advisory/ctac/workgroup/ProgramPlanning/Roster.pdf>.

⁹ Members are listed at <http://deainfo.nci.nih.gov/advisory/ctac/workgroup/CTpriority/Roster.pdf>.



2.2 COMPREHENSIVE PROCESS FOR TRIAL PRIORITIZATION

Over the course of the four meetings held from December 2013 to March 2014, a comprehensive process for trial prioritization was developed. The process has three components: prospective disease-specific priority setting, identifying trial categories generally considered either high or low priority and a cross-disease prioritization process to rank resource-intensive trials in priority order for funding, if NCTN resource constraints necessitate.

A. PROSPECTIVE DISEASE-SPECIFIC PRIORITY SETTING

The NCTN WG recommended that a process be implemented whereby strategic trial priorities for each disease are established prospectively and are used to guide both concept development and approval. The NCTN WG developed basic principles to govern this new approach as well as a framework for how the priority setting process should be conducted.

Basic Principles for Disease-Specific Priority Setting

Five basic principles to govern disease-specific priority setting were developed:

1. Strategic priorities are set in advance both to guide concept development and serve as one important criterion for the Scientific Steering Committees when evaluating concepts.
2. The majority of approved concepts are expected to align with the strategic priorities.
3. Concepts not aligned with the strategic priorities may still be approved but additional justification will likely be required.
4. NCTN Groups¹⁰ remain responsible for concept development.
5. Scientific Steering Committees continue to rigorously evaluate concepts for scientific and clinical quality, applying equally critical standards to concepts that are aligned with the strategic priorities as are currently applied in concept evaluation.

Process for Disease-Specific Priority Setting

The process for disease-specific priority setting envisioned by the NCTN WG evolved over the course of the various discussions and would entail the following:

1. Setting of strategic priorities would be conducted under the aegis of the Scientific Steering Committee for each disease area. This was judged the appropriate venue, since the Committee involves the disease-specific scientific leadership from all the relevant NCTN Groups as well as other disease experts, patient advocates, community oncologists, translational researchers, and NCI.
2. A strategic assessment of the clinical trials landscape within the disease would be prepared in advance to identify gaps and provide context for the priority setting process. This assessment would encompass

¹⁰ Whenever the term “NCTN Groups” is used in Section II of this report, it should be understood to encompass the NCORP Research Bases in the case of the SxQOL trial portfolio.



not only NCI funded trials but also available information about trials funded by industry, foundations and other government entities as well as international trials.

3. The NCTN Groups would be responsible for proposing strategic priorities for discussion, ideally generated from cross-NCTN Group collaboration. As appropriate, input would be requested from outside experts (e.g., from industry representatives, basic and translational researchers, international clinical researchers) when deliberating on these proposed priorities.
4. The goal of the priority setting exercise would be to select a few major priorities for each disease around which concepts should be developed.
5. The strategic priorities would be reviewed annually and revised as needed. This review would include an analysis of concepts approved in the past year for alignment with the strategic priorities as well as new clinical trial results and scientific advances which might lead to new priorities.

NCTN WG members noted that setting strategic priorities in advance would increase efficiency by helping investigators and the NCTN Groups understand early on which concepts would be more or less likely to be approved. WG members also stressed the importance of ensuring that the strategic priorities remain flexible so they can be easily updated in response to advances in the field. Finally, the group pointed out that the priority-setting process would probably need to be implemented somewhat differently for different diseases and that some Scientific Steering Committees already have experience in setting priorities while others do not.

B. HIGH AND LOW PRIORITY TRIAL CATEGORIES

In discussing the overall process of trial prioritization, several categories of trials emerged as being generally of either high or low priority for conduct within NCTN or NCORP.

High Priority Trial Categories

- Trials driven by the best current science
- Trials expected to substantially influence short- or long-term clinical or quality of life patient outcomes
- Trials responsive to NCI strategic priorities and initiatives (e.g., the MATCH¹¹ trial)
- Trials aligned with a disease-specific strategic priority
- Trials unlikely to be performed outside the NCTN or NCORP (e.g. surgery, radiation, rare diseases)

Low Priority Trial Categories

- Trials with non-inferiority trial designs
- Trials aimed at small differences in progression free survival or disease free survival
- Trials duplicative of ongoing or completed NCTN, NCORP, industrial and/or international trials
- Trials of “me-too” drugs

¹¹ MATCH stands for **M**olecular **A**nalysis for **T**herapy **C**hoice



While there was strong agreement with regard to the trial categories that should be considered high priority, NCTN WG members expressed some concern that there could be specific trials within the low priority categories that would be important for NCI to conduct. Therefore, WG members did not agree that all concepts for trials in the low priority categories should be automatically rejected. Instead, there was agreement that trials in the low priority categories should only be performed rarely and require a high bar for approval, including the potential for either a large, practice-changing outcome benefit or substantial scientific impact.

Moreover, there was considerable discussion about whether trials that take many years (e.g., >10 years) to achieve results should be considered low priority, and no consensus was reached. In particular, the concern was raised that in certain instances a clinical question can only be answered by conducting a very long trial with screening and chemoprevention trials being the most obvious, but not the only, examples. Therefore, while there was agreement that trials of long duration should be given extra scrutiny, there was a strong sentiment that for this trial category the decision should be made case-by-case based on the particulars of the trial question being addressed.

Finally, WG members pointed out that applying these general principles for trial categories of high and low priority across all diseases will require clear disease-specific operational definitions of terms, such as “substantial influence” and “small differences”, as the appropriate definition can vary from disease to disease.

C. CROSS-DISEASE PRIORITIZATION IN RESPONSE TO RESOURCE CONSTRAINTS

The final aspect of trial prioritization addressed by the NCTN WG was that of cross-disease prioritization. This aspect of prioritization is quite different in that it would only be invoked when NCTN resources are deemed insufficient to support trials for all approved concepts; whereas the other aspects of prioritization would be implemented on a continuous, ongoing basis. Moreover, because cross-disease prioritization is directly tied to resource availability, the conclusion was reached that it should not be applied to all trials but only to large (>1,000 patient) or otherwise resource intensive phase 3 trials.

The NCTN WG deliberations were greatly facilitated by the decision of NCI and the NCTN WG Chairs to pilot a cross-disease prioritization process in order to determine the feasibility of assessing scientific and clinical priority across diseases. To conduct the pilot, a CTAC Clinical Trials Prioritization WG of extramural cancer clinical trial experts was convened to evaluate the relative priority of two >1,000-patient Scientific Steering Committee approved concepts that were on hold because of potential 2014 funding constraints, using a defined set of criteria.

Basic Principles for Cross-Disease Prioritization

Five basic principles were developed to govern cross-disease prioritization:

1. Cross-disease prioritization should only be invoked in response to resource constraints, namely insufficient NCTN resources to support trials for all Scientific Steering Committee approved concepts.
2. Cross-disease prioritization should only be applied to resource-intensive trials.
3. Cross-disease prioritization should be implemented via priority ranking of Scientific Steering Committee approved concepts by extramural experts.
4. Cross-disease prioritization should be guided by specified criteria.



5. Results of the cross-disease prioritization process should represent only one aspect of the information NCI would use in deciding whether to proceed with a resource intensive trial.

The only aspect of these principles that was not fully clarified was a comprehensive operational definition of “resource-intensive” trials. While there was agreement that trials with >1,000 patients should be considered resource intensive, no consensus was reached on other resource-intensive attributes that might trigger cross-disease prioritization. Other potential resource-intensive attributes discussed included the following: use of a complex screening algorithm; high projected accrual rate (accrual per month or year); large number of non-standard procedures, data points and/or correlative studies; and >10 years for accrual and follow-up.

Criteria for Cross-Disease Prioritization

Criteria for cross-disease prioritization were developed and refined over the course of the four meetings, resulting in the following set of recommended criteria.

Recommended Cross-Disease Prioritization Criteria
<p>Primary criteria</p> <ul style="list-style-type: none"> • Clinical benefit/importance • Scientific impact/contribution
<p>Secondary criteria</p> <ul style="list-style-type: none"> • Patient/public health need • Relationship to current clinical trials landscape • Procedural complexity (includes size and cost) • Feasibility of accrual • Suitability for NCTN Program • Alignment with overall NCI scientific initiatives • Ability to leverage non-NCI funds

Cross-disease Prioritization Pilot Process

Prior to the Cross-Disease Prioritization Pilot, primary, secondary, biostatistical and advocate discussants were assigned to each concept. During the meeting, discussion of each concept began with background information and comments provided by NCI staff from CTEP. The primary discussant then provided their analysis of the concept, followed by any additional comments from the secondary, biostatistical, and advocate discussants. Following these presentations, an open discussion of the concept was conducted. Following the discussion, participants confidentially assigned scores for each criterion as well as an overall score. The participants then reviewed the de-identified and collated results to determine if the scores and relative ranking of the two concepts reflected the discussion and the perceived relative strength of the concepts.

Assessment of the Cross-Disease Prioritization Pilot

The Clinical Trials Prioritization WG concluded that the piloted process for cross-disease prioritization was both appropriate and feasible. However, the group also stressed the importance of keeping the process at a high level and guarding against allowing cross-disease prioritization to become another layer of scientific review or concept redesign. Other comments and suggestions on various aspects of the process are summarized below.

Composition of the Prioritization Group

The Prioritization WG concluded that the individuals assembled for the pilot represented the correct mix of high level expertise, experience, and responsibilities to conduct cross-disease prioritization. They also agreed that the



involvement of additional disease-specific experts (e.g., concept Principal Investigator, Scientific Steering Committee Chair) was not necessary. Finally, the group suggested that there be substantial overlap in the individuals asked to participate in different prioritization rounds, rather than convening a totally new group of individuals each time it is necessary to prioritize across diseases. This was viewed as both more efficient and more likely to provide consistent results across prioritization rounds.

Prioritization Process

The Prioritization WG also recommended two improvements to the cross-disease prioritization process based on the pilot. First, the group suggested providing the prioritization body with information about disease-specific priorities and identified gaps across all diseases, as well as the current resource allocation by disease. They felt that this information would be valuable in judging whether a particular resource intensive concept addresses an especially important priority or need in the context of the overall NCTN trial portfolio. Secondly, the group suggested using a 5-point scale for scoring both the individual criteria and providing an overall rating.

Implementation Concerns

The Prioritization WG stressed three concerns with implementation of a cross-disease prioritization process:

1. It is important to proactively and clearly communicate to external stakeholders that the cross-disease prioritization process will affect only a very small number of resource-intensive trials and will be invoked sparingly.
2. There is a need for clarity on whether trials that NCI decides not to fund based on the cross-disease prioritization, are permanently “off the table” or could potentially be funded at a later date if resources become available.
3. It is necessary to reduce the potential negative impact of the process by announcing well in advance if there are restrained resources which might cause Scientific Steering Committee approved resource intensive trials to not be funded. This would allow investigators and the NCTN Groups to make an informed judgment about whether or not to devote effort to developing a concept for a resource intensive trial ideas.



2.3 PERIODIC STRATEGIC ASSESSMENT OF TRIAL PORTFOLIOS

The NCTN WG recommended that a periodic strategic assessment of each trial portfolio, similar to the portfolio assessment conducted by the NCTN WG from July 2012 to July 2013, be conducted as a complement to prospective priority setting and cross-disease prioritization.

Value of Periodic Portfolio Assessment

The NCTN WG concluded that the portfolio assessment process conducted from July 2012 to July 2013 was useful for evaluating both the quality of the trial portfolios and NCTN Group, NCORP Research Base and Scientific Steering Committee processes for concept development and evaluation, respectively. The NCTN WG process was viewed as focusing the attention of both the NCTN Groups, the NCORP Research Bases and the Scientific Steering Committees on the strengths and weaknesses of their trial portfolios and their processes for concept development and evaluation. It was also pointed out that the portfolio assessment has already resulted in improvements to Group, Research Base and/or Steering Committee processes for certain portfolios.

Recommended Portfolio Assessment process

Assessment Group Membership

An assessment group similar in composition the NCTN WG was recommended. However, it was suggested that NCI consider including one Chair from each Scientific Steering Committee, as well as increasing the number of Cancer Center Directors in future assessment groups. In addition, it was suggested that NCI consider including Group Disease Committee Chairs (or NCORP Research Base Committee Chairs) in the assessment group when their portfolio was being evaluated.

Assessment Activities

The assessment was proposed to encompass three major activities.

1. **In depth assessment of the trial portfolios:** The assessment would be designed to assess the quality of active ongoing trials and the alignment of those trials with portfolio-specific strategic priorities. If needed based on the results, advice would also be provided on ways to improve the effectiveness of the relevant NCTN Group Disease Committees, NCORP Research Base Committees and/or Scientific Steering Committee.
2. **Cross-portfolio assessment:** The assessment would also examine the balance of trial activity across portfolios and identify cross-portfolio synergies (e.g., trials addressing common pathways, high throughput diagnostics, functional imaging correlates). Additionally, the assessment process would provide a forum for sharing best practices, such as trial designs, accrual strategies, and Scientific Steering Committee policies and procedures.
3. **Portfolio recommendations:** As needed based on the results, strategic recommendations would be developed for improving the individual portfolios and/or the overall NCTN/NCORP trial portfolio. These recommendations would be communicated to the NCTN Groups, the NCORP Research Bases the Scientific Steering Committees, NCI leadership and CTAC.

Scope of Portfolios Assessed



The original proposal was to only assess a portion (e.g. one-third) of the portfolios each year. However, some concerns were raised about considering only one-third of the portfolios each year, due to the perceived value in having a complete picture of the overall NCTN/NCORP portfolio. Additionally, some members noted that reviewing all portfolios might be important for facilitating the evolution from organizing around disease sites to organizing around biological pathways. The WG also suggested that if assessments are to be performed on an ongoing basis, it might be advisable only to evaluate portfolio perceived as experiencing difficulties.

Timing of Assessment

The WG recommended that at least one more comprehensive portfolio assessment be conducted in order to determine the impact of the NCTN WG process and the resulting recommendations. However, the NCTN WG members did not reach consensus on whether the next set of portfolio assessments should begin in 2015 or in 3 years. Those in favor of beginning assessments in 2015 pointed out that if assessments were not conducted again until 2017, the portfolios examined first (July 2012) would not be re-examined for 5 years. In addition, they felt it would be valuable to have Scientific Steering Committee Chairs and NCTN Groups/NCORP Research Bases report back in 2015 on their progress in implementing recommendations from the initial portfolio assessment. In contrast, those in favor of waiting until 2017 argued that the Scientific Steering Committees and NCTN Groups/NCORP Research Bases may not have had enough time to implement changes by 2015. There was also not consensus on the optimal periodicity if portfolio assessments were to be conducted on an ongoing basis. Some argued that assessment every 3 years was necessary to preserve institutional memory and momentum. Others stated that 5 years might be more appropriate given the speed with which the science often moves and the time that might be required to implement recommended changes.



Section III

Appendices



3.1 NCTN WORKING GROUP PARTICIPANT LIST

Chairs

Robert B. Diasio, M.D.

Professor of Molecular Pharmacology and
Experimental Therapeutics and Oncology
Director
Mayo Clinic Cancer Center
Rochester, MN

George W. Sledge, Jr., M.D.

Chief of Oncology
Department of Medicine, Oncology
Stanford University, School of Medicine
Stanford, CA

Participants

Peter C. Adamson, M.D.

Chair
Children's Oncology Group
Professor of Pediatrics
Perelman School of Medicine
University of Pennsylvania
Philadelphia, PA

Monica M. Bertagnolli, M.D.

Chair
Alliance
Professor of Surgery Harvard Medical School
Brigham & Women's Hospital
Dana-Farber Cancer Institute
Boston, MA

Robert J. Arceci, M.D., Ph.D.

Professor of Pediatrics
Phoenix Children's Hospital
University of Arizona College of Medicine
Phoenix, AZ

Michael Birrer, M.D., Ph.D.

Professor
Department of Medicine
Harvard Medical School
Boston, MA

James N. Atkins, M.D.

Principal Investigator
Southeast Cancer Control Consortium, CCOP.
Winston-Salem, NC

Charles D. Blanke, M.D.

Chair-Elect
SWOG
Professor of Medicine
Hematology and Medical Oncology
Knight Cancer Institute
Oregon Health & Science University
Portland, OR

Gerold Bepler, M.D., Ph.D.

President and CEO
The Barbara Ann Karmanos Cancer Institute
Wayne State University School of Medicine
Detroit, MI

Deborah Watkins Bruner, Ph.D., RN, FAAN

Professor of Nursing
Emory's Nell Hodgson Woodruff School of Nursing
Emory University
Atlanta, GA



Thomas A. Buchholz, M.D., F.A.C.R.

Department Chair
Department of Radiation Oncology
Division Head
Division of Radiation Oncology
The University of Texas MD Anderson Cancer Center
Houston, TX

Robert L. Comis, M.D.

Chair
ECOG
Professor of Medicine and Director
Drexel University Clinical Trials Research Center
Philadelphia, PA

Joseph P. Costantino, Dr.P.H.

Group Statistician
NSABP
University of Pittsburgh
Pittsburgh, PA

Walter J. Curran, Jr., M.D.

Chair
RTOG
Executive Director
Winship Cancer Institute
Lawrence W. Davis Professor & Chairman
Department of Radiation Oncology
Emory University
Atlanta, GA

Robert S. DiPaola, M.D.

Director
The Cancer Institute of New Jersey
New Brunswick, NJ

Elizabeth Eisenhauer, M.D., F.R.C.P. (C)

Interim Director, NCIC CTG
Cancer Clinical Trials Division
Cancer Research Institute
Queen's University
Kingston Ontario Canada

Michael J. Fisch, M.D., M.P.H.

Co-Chair SxQOL SC
Associate Professor, General Oncology
The University of Texas MD Anderson Cancer Center
Houston, TX

Jeffrey P. Krischer, Ph.D.

Principal Investigator
Sun Coast CCOP Research Base
University of South Florida
Tampa, FL

Anne-Marie R. Langevin, M.D.

Principal Investigator
South Texas Pediatric MB-CCOP
University of Texas Health Science Center
San Antonio, TX

Steven M. Larson, M.D.

Vice Chair for Research
Donna & Benjamin M. Rosen Chair
Department of Radiology
Memorial Sloan Kettering Cancer Center
New York, NY

Michael LeBlanc, Ph.D.

Group Statistician
SWOG
Professor
Department of Biostatistics
University of Washington
Seattle, WA

Frank L. Meyskens, Jr., M.D.

Director
Chao Family Comprehensive Cancer Center
University of California, Irvine
Associate Chair
Cancer Control and Prevention
SWOG
Irvine, CA



Neal J. Meropol, M.D.

Dr. Lester E. Coleman, Jr. Professor of Cancer Research and Therapeutics
Chief, Division of Hematology and Oncology
Associate Director for Clinical Research
Case Comprehensive Cancer Center
Associate Director for Clinical Programs, University Hospitals Seidman Cancer Center
Cleveland, OH

Nikhil C. Munshi, M.D.

Associate Professor of Medicine
Harvard Medical School
Dana-Farber Cancer Institute
Boston, MA

Nancy Roach

Consumer Advocate
C3: Colorectal Cancer Coalition
Hood River, OR

Daniel J. Sargent, Ph.D.

Group Statistician
Alliance
Director
Cancer Center Statistics
Mayo Clinic Cancer Center
Rochester, MN

Mary Lou Smith, J.D., MBA

Consumer Advocate
Co-founder
Research Advocacy Network
Plano, TX

Joel E. Tepper, M.D.

Hector MacLean Distinguished Professor of Cancer Research
Department of Radiation Oncology
Lineberger Comprehensive Cancer Center
University of North Carolina
Chapel Hill, NC

George J. Weiner, M.D.

C.E. Block Chair of Cancer Research
Professor
Department of Internal Medicine
Director Golden Comprehensive Cancer Center
University of Iowa
Iowa City, IA

Cheryl L. Willman, M.D.

Professor of Pathology & Medicine
Director and CEO
University of New Mexico Cancer Center
Albuquerque, NM

Robin T. Zon, M.D., F.A.C.P.

Principal Investigator
Northern Indiana Cancer Research Consortium
South Bend, IN

NCI and Science and Technology Policy Institute Liaisons

Jeffrey S. Abrams, M.D.

Associate Director
Cancer Therapy Evaluation Program
Division of Cancer Treatment and Diagnosis
National Cancer Institute
National Institutes of Health
Bethesda, MD

James H. Doroshow, M.D.

Deputy Director
Clinical and Translational Research
National Cancer Institute
National Institutes of Health
Bethesda, MD



Leslie G. Ford, M.D.

Associate Director for Clinical Research
Office of the Director
National Cancer Institute
National Institutes of Health
Bethesda, MD

Judith Hautala, Ph.D

Research Staff Member
Science and Technology Policy Institute
Washington, DC

Worta McCaskill-Stevens, M.D., M.S.

Program Director
Minority-Based Community Clinical Oncology
Program
Division of Cancer Prevention
National Cancer Institute
National Institutes of Health
Bethesda, MD

Lori Minasian, M.D., FACP

Deputy Director
Division of Cancer Prevention
National Cancer Institute
National Institutes of Health
Bethesda, MD

Margaret M. Mooney, M.D., MBA

Branch Chief
Clinical Investigations Branch
Cancer Therapy Evaluation Program
Division of Cancer Treatment and Diagnosis
National Cancer Institute
National Institutes of Health
Bethesda, MD

Sheila A. Prindiville, M.D., M.P.H.

Director
Coordinating Center for Clinical Trials
Office of the Director
National Cancer Institute
National Institutes of Health
Bethesda, MD

Executive Secretary

Deborah R. Jaffe, Ph.D.

Program Director
Coordinating Center for Clinical Trials
Office of the Director
National Cancer Institute
National Institutes of Health
Bethesda, MD



3.2 ACRONYMS

ALL	Acute Lymphoblastic Leukemia
AML	Acute Myeloid Leukemia
BCSC	Breast Cancer Scientific Steering Committee
BIQSFP	Biomarker, Imaging, & Quality of Life Studies Funding Program
BMSC	Brain Malignancy Steering Committee
CCCT	NCI's Coordinating Center for Clinical Trials
CCOP	Community Clinical Oncology Program
CISC	Clinical Imaging Steering Committee
CLL	Chronic Lymphocytic Leukemia
CML	Chronic Myelogenous Leukemia
COG	Children's Oncology Group
CRC	Colorectal cancer
CTAC	Clinical Trials and Translational Research Advisory Committee
CTPM	Clinical Trials Planning Meeting
DCP	NCI's Division of Cancer Prevention
DCTD	NCI's Division of Cancer Treatment and Diagnosis
EBV	Epstein-Barr Virus
GCSC	Gynecologic Cancer Steering Committee
GI	Gastrointestinal
GISC	Gastrointestinal Scientific Steering Committee
GOG	Gynecologic Oncology Group
GU	Genitourinary
GUSC	Genitourinary Scientific Steering Committee
HPV	Human Papillomavirus
LKSC	Leukemia Scientific Steering Committee
LYSC	Lymphoma Scientific Steering Committee
MYSC	Myeloma Steering Committee
NCI	National Cancer Institute
NCORP	NCI Community Oncology Research Program
NCTN	NCI National Clinical Trials Network



NCTN WG	NCI National Clinical Trials Network Working Group
NIH	National Institutes of Health
PLLSC	Pediatric Leukemia and Lymphoma Steering Committee
QOL	Quality of Life
SPORE	Specialized Programs of Research Excellence
SxQOL	Symptom Management and Health-Related Quality of Life
TCGA	The Cancer Genome Atlas
TF	Task Force
TMSC	Thoracic Malignancy Steering Committee
WG	Working Group



3.3 SAMPLE BALLOT

Evaluation of Approved _____ Cancer Studies in Portfolio

1) Enter your assigned number: _____

Please rate the approved studies listed below on the five criteria and provide an overall score using the guideline below.

Rating / Score of Potential Importance and Impact on Standard of Care	Rating / Score Description (Dec 2012)	Rating / Score Description (Mar and July 2013)
High	High	Outstanding-Excellent
Medium	Medium	Very Good-Satisfactory
Low	Low	Fair-Poor

Please note that the overall score for a concept does not have to be an average. There is no specific weight for any criteria. Each person may give more or less weight to the criteria using their own best judgment to determine the overall score for each concept.

2) Score each approved concept in the _____ portfolio on the five criteria and provide an overall concept score:

	Five Individual Criteria					OVERALL Concept Score
	Feasibility	Clinical Importance	Scientific Contribution	Manageable Cost/Resource Burden	Unique Suitability for NCTN Program	
Concept 1						
Concept 2						
Concept 2						
Concept 4						
Concept 4						
Concept 5						
Concept 6						

3) Overall _____ Portfolio Recommendations: