Presentation to NCAB Clinical Trials Subcommittee on Clinical Investigations on NCTN Performance Survey

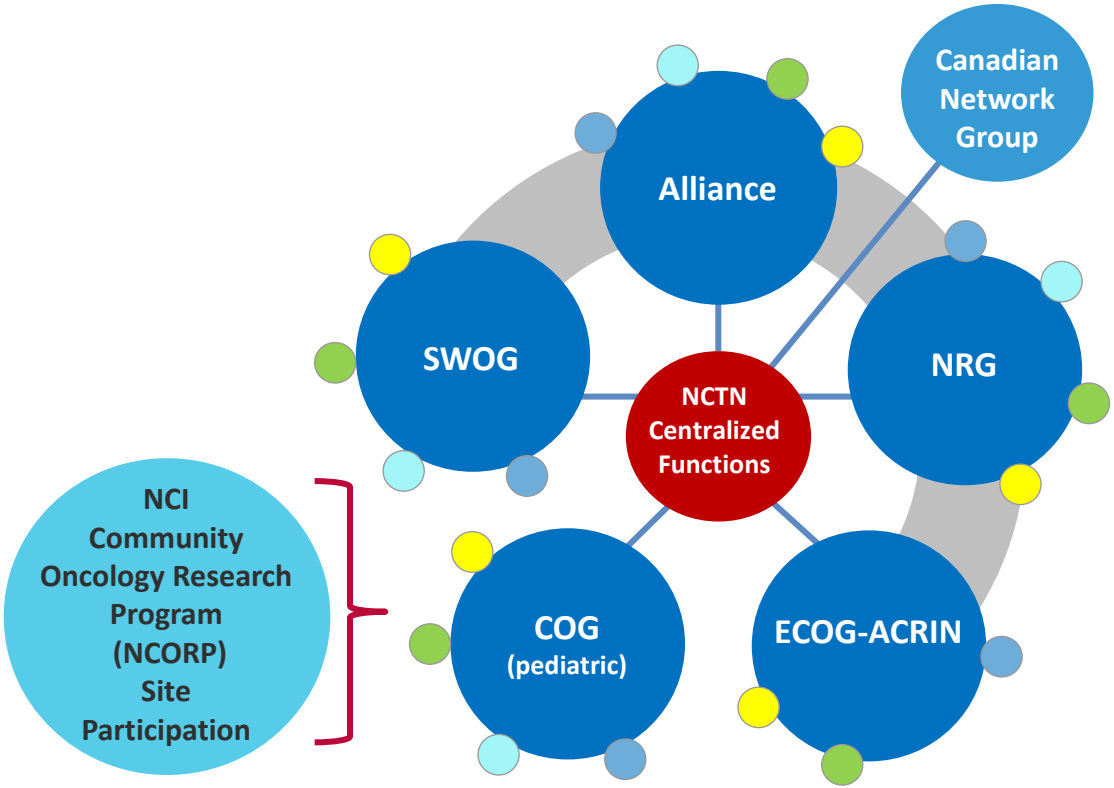
(March 2019 to July 2022)

NCI National Clinical Trials Network (NCTN)

Established in 2014 *from former NCI Cooperative Group Program with the following objectives:*

- Establish & support an infrastructure designed to harmonize processes and promote collaborations for the NCTN to reinvigorate the clinical trials portfolio to:
  - Continue focus on questions not well supported in commercial environment
  - Prioritize trials & incorporate innovative science & design into clinical trials
  - Provide a functional platform to perform large scale testing of increasingly smaller subsets of molecularly-defined cancers and incorporate "*precision medicine trials"* into portfolio along with trials in rare tumors
  - Maintain a commitment to the conduct of trials in special populations
  - Emphasis on late-phase clinical trials (phase 3 and phase 2 trials)

NCTN Organization and Infrastructure



≈ 2,200 enrolling sites across North America plus international sites

LEGEND:

Centralized Functions:
- NCI Central IRB with 4 Boards
- Cancer Trials Support Unit for Administrative & Regulatory Functions
- RT/Imaging Core Center
- NCI Disease Steering Review Committees
- Common Data Mgt w/ Central Hosting

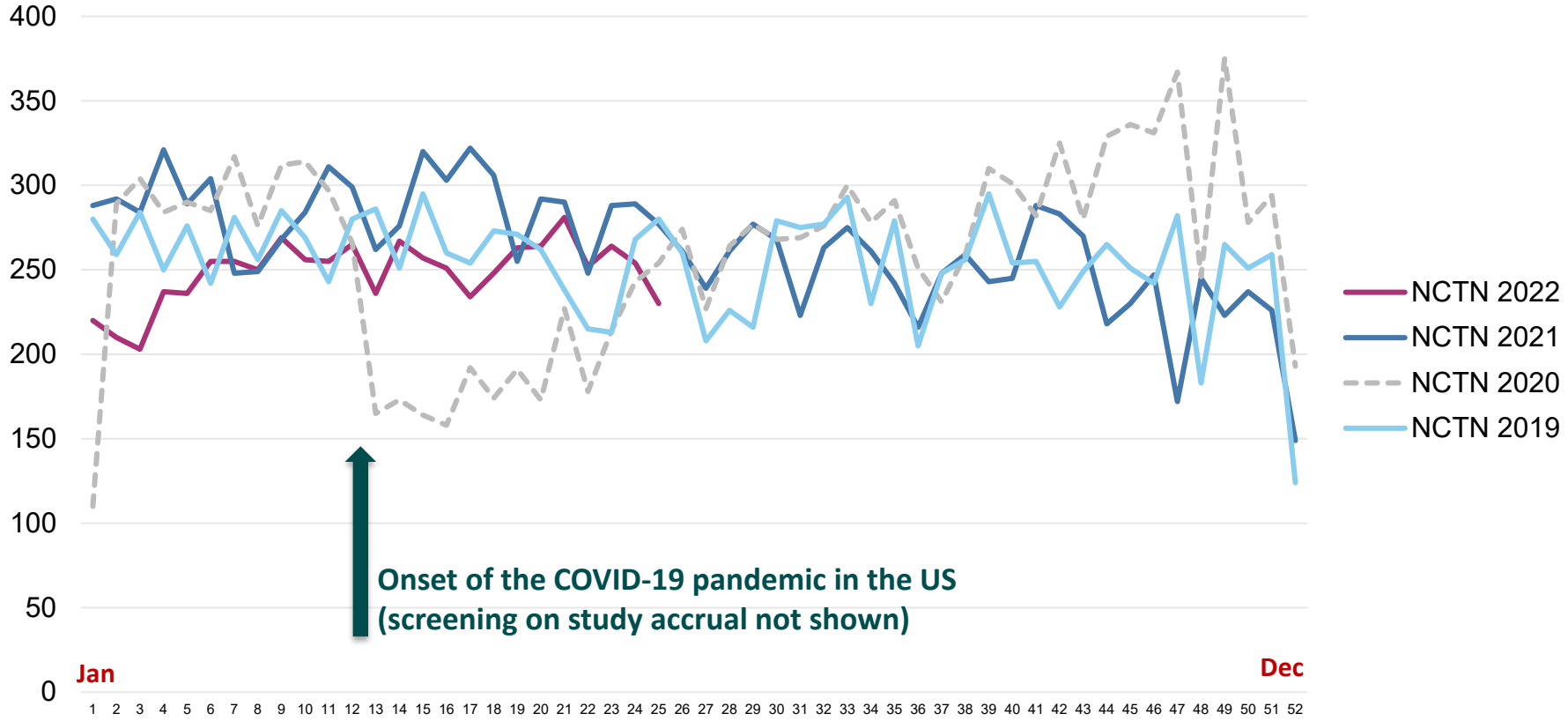
Lead Academic Participating Sites (LAPS)

Operations Centers

Statistics & Data Management

Tumor Banks

Weekly Intervention/Other Accrual in the NCTN 2019-2022 as of June 30, 2022



In preparation for assessment of the NCTN Program for re-competition, a survey of Key Leaders in the NCTN/NCORP participating in NCTN Trials was conducted to provide input on current network performance

Responses to Questions on the
NCTN Performance Survey on Current Project Period
(March 2019 to July 2022)

Survey:
Development, Participants, Distribution/Response

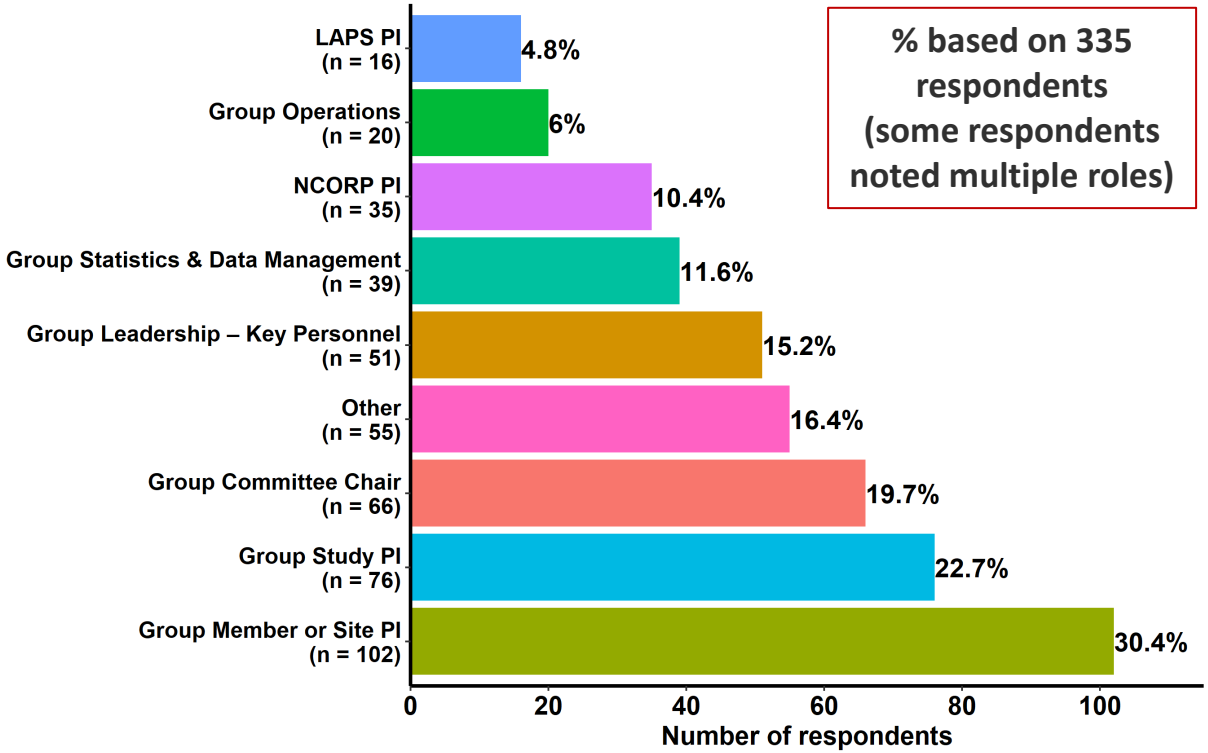
- **Development**: Based on previous 2016-2017 survey & developed & edited by NCI staff & NCTN Group leadership - Approved under OMB Clearance No. 0766

- **Participants:** Key NCTN Group participants, Lead Academic Participating Site (LAPs) PIs and NCORP PIs and key admin listservs

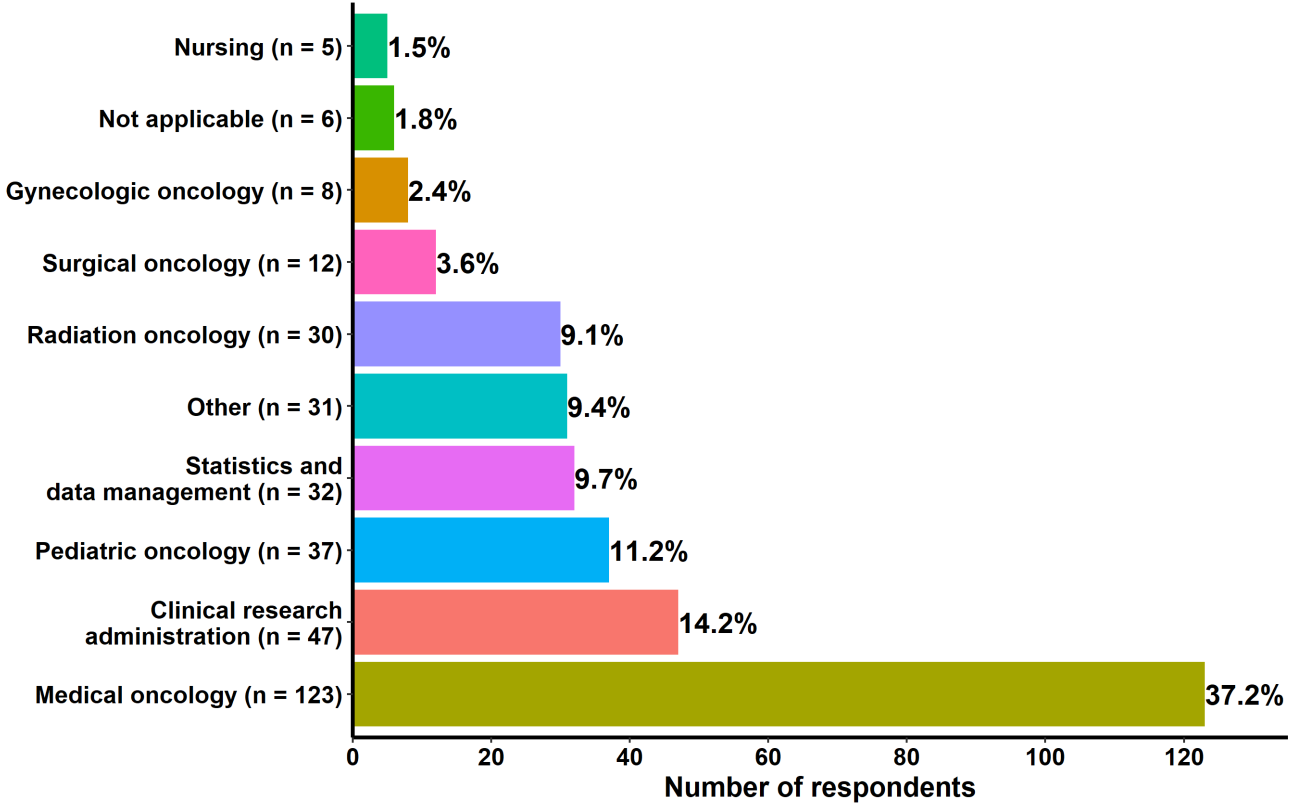
- **Distribution/Response:** Survey open 32 days: July 25 to August 26, 2022
  - Number who started the survey: **335**
  - Number who completed the "overall satisfaction" question: **272**
  - Drop-off from first to last survey question: **254**
  - Comments**:** **214** respondents provided 799 meaningful comments (i.e., not "Nothing to add" or "N/A") to ≥ 1 question (80% of 272 who answered "overall satisfaction" question)

Respondents by Group Affiliation & Role (n=335)

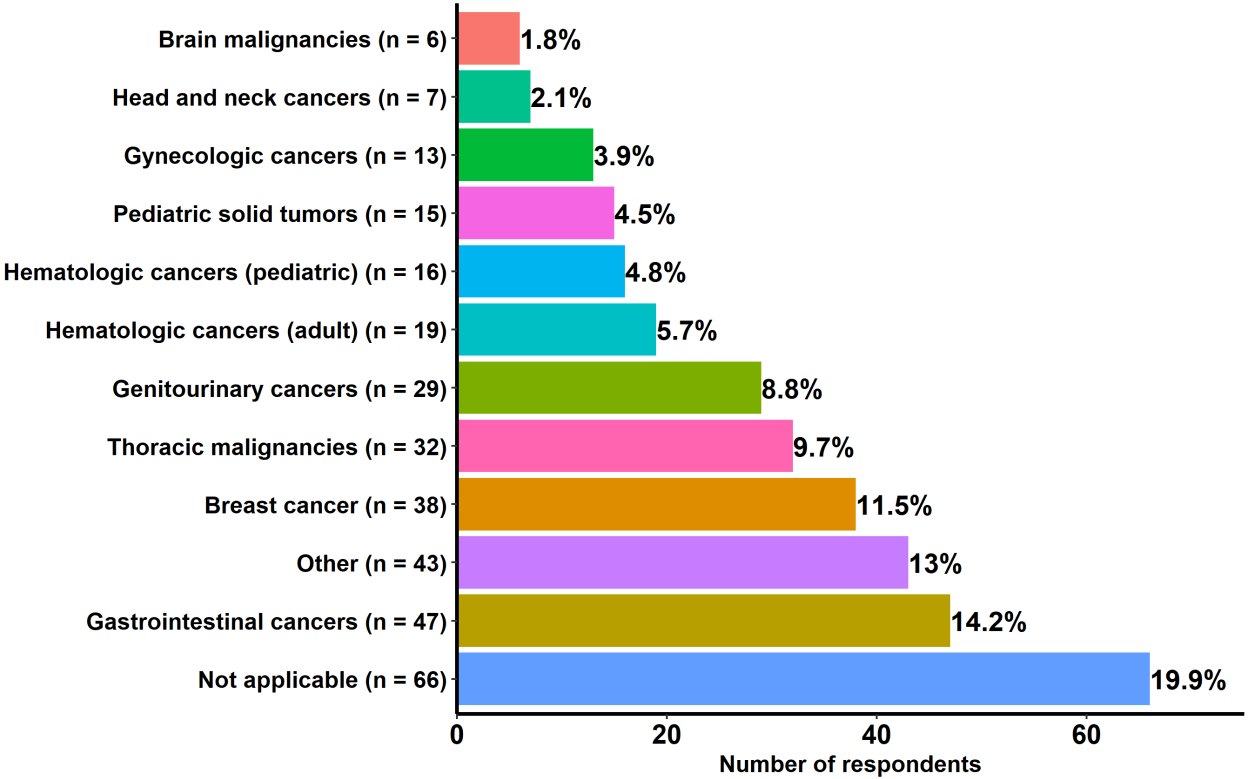
NCTN Group(s) Affiliation	# Respondents (could select multiple)	% of Total Respondents (% of n=335)
Alliance	161	48.1
COG	82	24.5
ECOG-ACRIN	137	40.9
NRG	167	49.8
SWOG	134	40.0
Canadian CTG	38	11.3



Respondents by Primary Area of Expertise
Number of respondents = 331

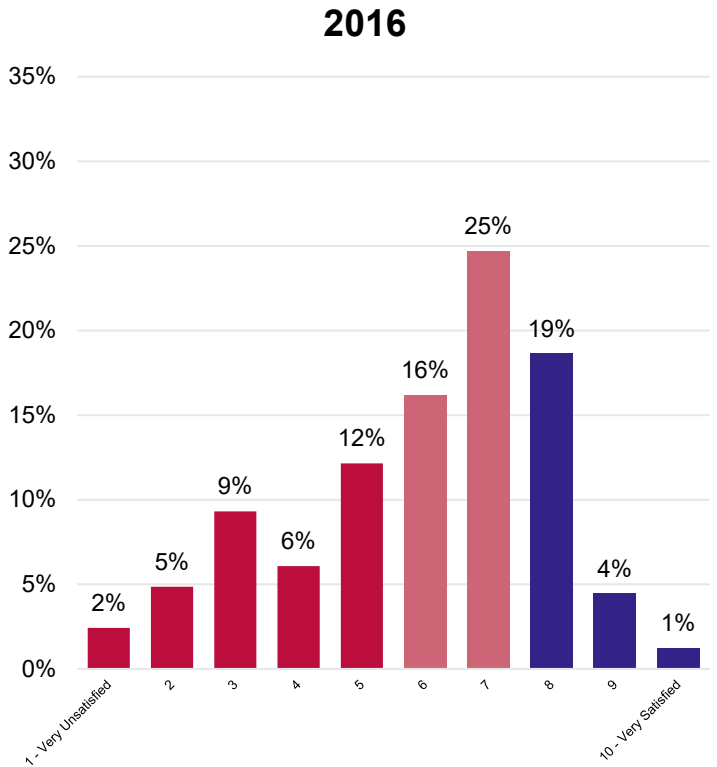


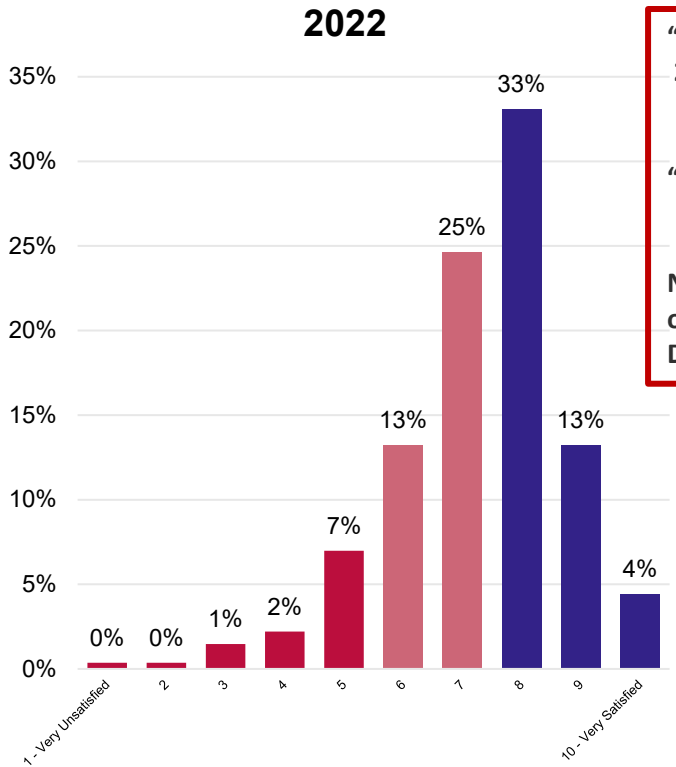
Respondents by Primary Area Disease
Number of respondents = 331



Context: Satisfaction Has Improved

Overall Satisfaction with the NCTN: December 2016 vs. August 2022



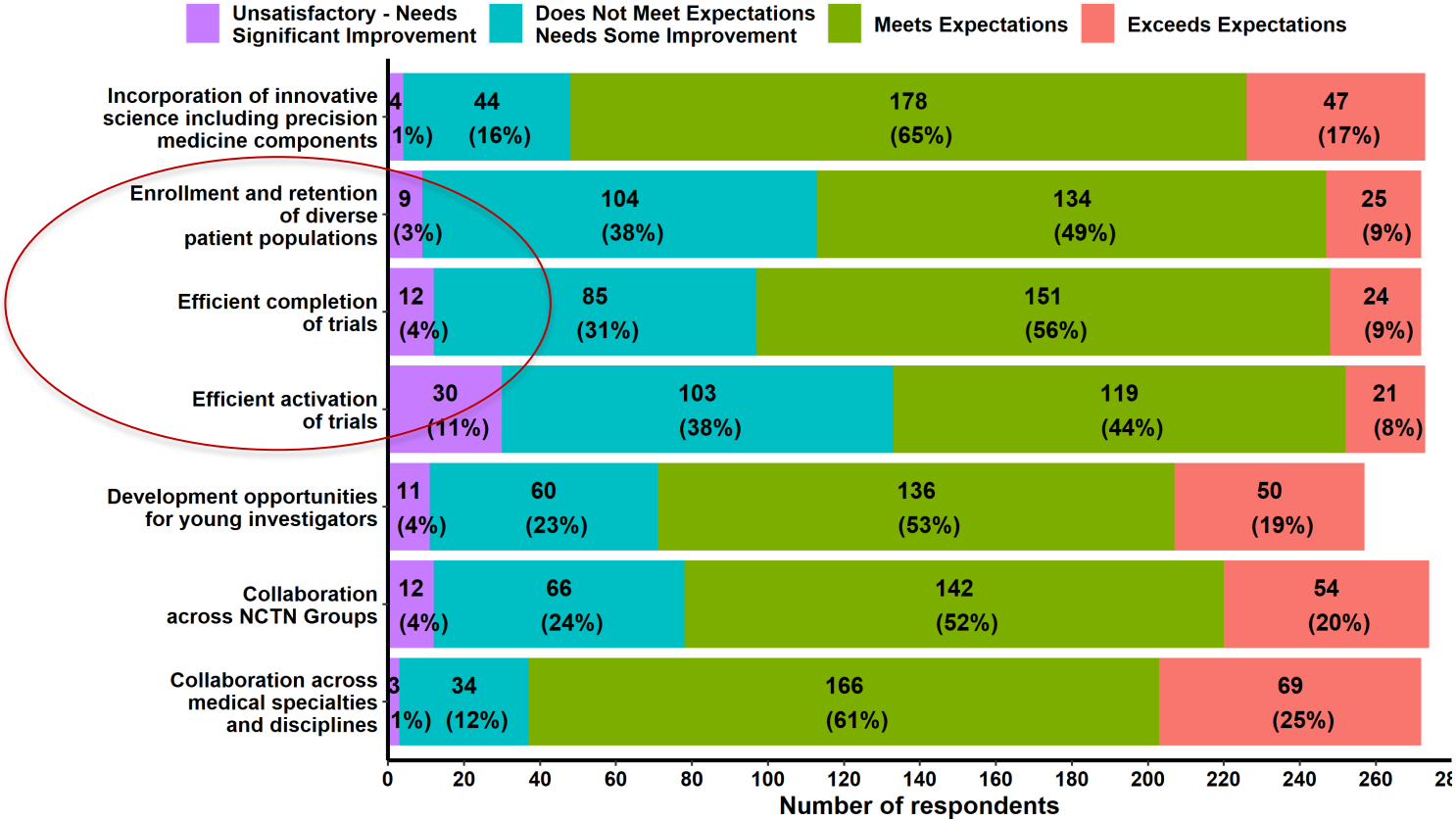


"Satisfied" range (6-10)
2016: 65% → 2022: 89%

"Very satisfied" range (8-10)
2016: 24% → 2022: 51%

No differences noted based on Group Affiliation, Role, or Disease Area for 2022

Overall, how satisfied are you with the degree to which the NCTN is achieving the following goals? (n~270)



Context:
Minority Accrual NCTN & NCORP Clinical Trials All Phases

Minority Accrual (Numbers)								
	1999 - 2001	2002-2004	2005-2007	2008-2010	2011-2013	2014-2016	2017-2019	Total 1999-2019
Majority	85,424	104,766	77,936	74,616	63,570	49,968	58,707	514,987
Minority	**13,784**	**20,947**	**16,020**	**18,610**	**17,098**	**15,235**	**21,125**	**122,819**
Hispanic or Latino*	**4,099**	**6,650**	**5,475**	**6,687**	**6,485**	**6,051**	**8,235**	**43,682**
Unknown/ Not Reported	2,044	2,247	2,276	2,887	1,912	2,878	3,110	17,354
Total	101,252	127,960	96,232	96,113	82,580	68,081	82,942	655,160

Minority Accrual (Percentages)								
	1999 - 2001	2002-2004	2005-2007	2008-2010	2011-2013	2014-2016	2017-2019	Total 1999-2019
Majority	84%	82%	81%	78%	77%	73%	71%	78%
Minority	**14%**	**16%**	**17%**	**19%**	**21%**	**22%**	**25%**	**19%**
Hispanic or Latino*	**4%**	**5%**	**6%**	**7%**	**8%**	**9%**	**10%**	**7%**
Unknown/ Not Reported	2%	2%	2%	3%	2%	5%	4%	3%

A 20-Year View:
Accrual 1999-2019 as reported using OMB categories

Accrual of Minorities into NCTN and NCORP Clinical Trials: A Twenty-Year View Worta McCaskill Stevens, MD, MS, Presentations from the 2nd Joint Meeting of the NCI Board of Scientific Advisors (BSA) and the National Cancer Advisory Board (NCAB) - June 15, 2020

Increase Enrollment of Diverse Populations

Themes from the qualitative comments on how to improve diversity in trials:

- **Support program development at sites where the most vulnerable patients are getting care**, often not at cancer-specific centers
- Help sites that do not already have a robust research program through reducing workload and amount of expertise required to conduct studies
- **Standardize processes** and centralize aspects of trials as much as possible
- **Reduce amount of data** required for collection
- Allow wider parameter windows for follow up or visits as sometimes patients with low SES have trouble getting to the clinic
- Allow more remote/virtual collection of data without a need of an in- person exam
- Allow standard of care aspects of a trial to be delivered in the community whenever possible

Suggestions to Improve Enrolling Site Experiences

- **More complex systems & regulatory requirements straining staff & resources**
  - Regulatory mandates and duplicative data entries were cited as causing sites to spend more time "complying than enrolling."
- **Greater consistency and more centralized resources can help sites succeed**
  - Studies are asking for more and more (more data, more specimens, more reporting, etc.) but **help is needed to streamline these requests to make them more manageable for site research staff,** including document aids such as:
    - Visit checklists or Visit calculators to eliminate scheduling
    - Answers to "Frequently Asked" protocol questions
    - Greater compensation for staff time/energy
    - Common guidelines for NCTN groups with same core policies and procedures in protocol design templates, audits, documentation prep for remote audits, data entry folders in RAVE for studies, common shipping guidelines, to maximize efficiencies & reduce redundancies

Context: OEWG Timelines for Study Activation

NCI National Clinical Trials Network (NCTN)

Timeline Start: Date on Initial Review
Timeline End: Date of Activation
Timeline is in Calendar Days

Study Phase	Concept Approval (# Days)	Protocol Authoring & Submission (# Days)	Protocol Approval & Activation (# Days)	Total Timeline (Absolute Deadline)
NCTN Letter of Intent (All Phase 1 & Small Adult Phase 2 Trials)	60	60	280	400
NCTN Concepts (All Pediatric Phase 2 & Larger Adult Phase 2 Trials) (*)	60	60	330	450
NCTN Concepts (All Phase 2/3 and Phase 3 Trials) (*)	90	90	360	540

(*) Concepts are evaluated by NCI Disease-Specific Steering Committees
Note: Disposition of Phase 1/2 Trials depend on total size of trial

Interest in Streamlining & Increasing Collaboration for Trial Development

Themes from the qualitative comments on how to increase collaboration for NCTN trials:

- **Formalization of intergroup disease-based working committees** has helped with coordination of new studies between the groups
- **A system to recognize participants from multiple NCTN groups as the level of PI**, first or senior author on publications
- **Have regular intergroup meetings** to ensure protocols do not compete & they address the most pressing questions
- **Continue cultural changes to enhance collaborative** rather than competitive interactions between groups
- **Streamline evaluation processes to encourage innovation** & reduce risk that a novel/collaborative studies testing some new will not be incorporated into a trial

Increase Communication and Sharing of Best Practices

Consider annual “all Group” meetings or leadership teams to:

- **review current and upcoming trial portfolios, processes, & learn from each other** for best practices with brainstorming about areas of collaboration
- **provide mutual feedback/ideas of what is working/not working** as well as information from the NCTN on any new initiatives/ideas
- **allow NTCN groups to showcase their work**, discuss collaborations, and network
- **foster understanding** about what each NCTN group is doing (“time to share the good, the bad and the ugly”)

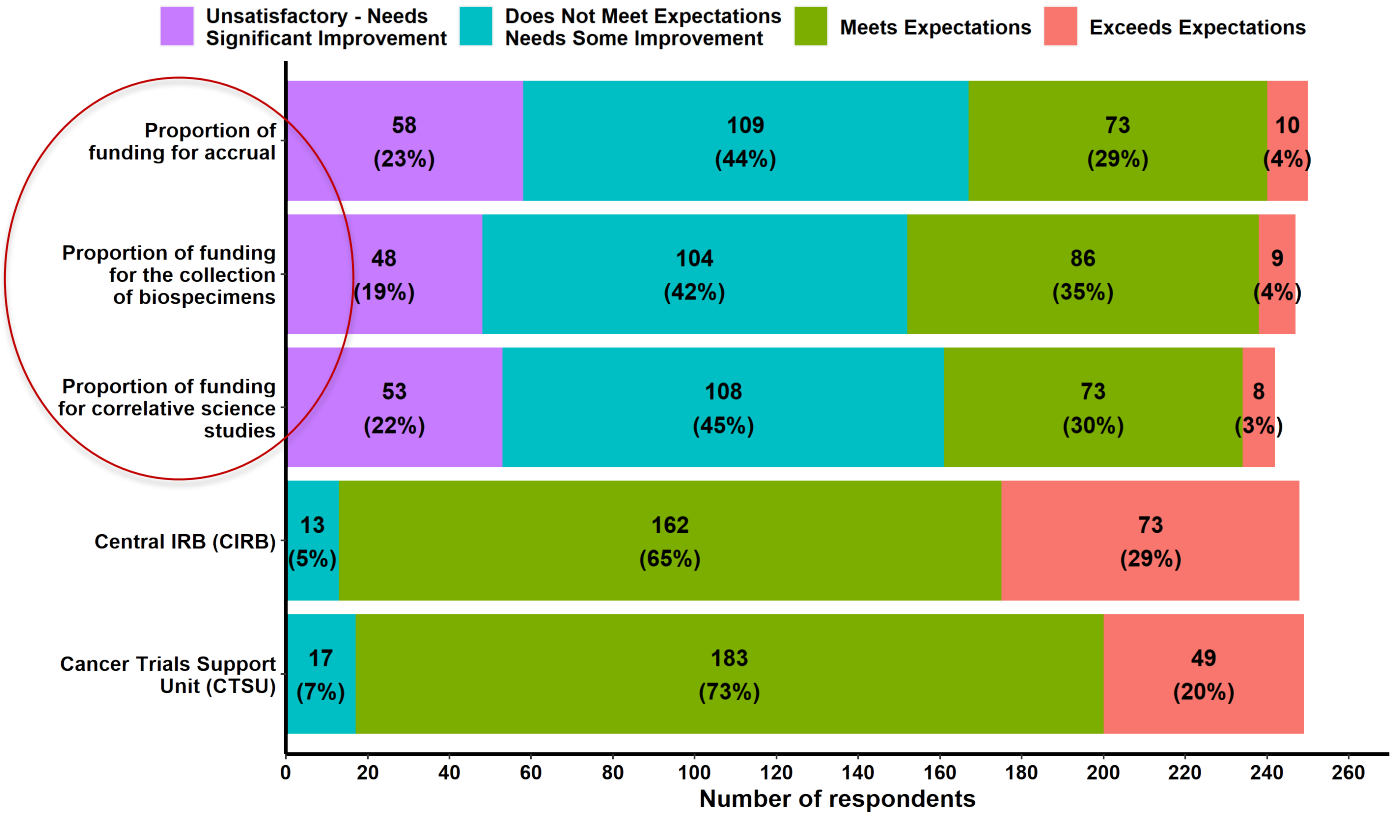
Suggestions to Improve Investigator Experiences

Reduce Risk of Stagnation, Increase Opportunities for Junior Investigators

Themes from the qualitative comments on how to increase opportunities for Junior Investigators:

- Suggestion to limit individuals to chairing only 1 study at a time, reducing/eliminating concurrent roles
- Consider term limits on committee chair roles where they are not already in place & require vice-chairs (study or committee) to be junior investigators, for example
- **Provide for more guidance / mentorship than already exist** to help produce trial concepts likely to succeed and providing guidance on what leads to good proposals, reducing wasted hours of investigator time

Overall, how satisfied are you with the following centralized services & administrative aspects of the NCTN? (n~250)



Context: Per Case Funding/Capitation to Sites

NCI National Clinical Trials Network (NCTN)

Trial Type	Funding Start Date	Basic Per-Case Site Payment	Basic Per-Case "High Performance" Equivalent Site Payment (*)
All Studies	Pre-2014 (1999-2014)	$2,000 (Plus F/U)	N/A
All Studies	NCTN Initial Project Period 2014	$2,250	$4,000
Non-IND Studies	NCTN Second Project Period 2019	~ $2,700	~ $4,300
IND Studies	NCTN Second Project Period 2019	~ $3,000 to $3,600	~ $4,600 to $5,200

Additional funding is provided for collection of biospecimens,, and scans for integral/integrated central review as well as embedded QOL.

(*) High Performance sites are LAPs and High-Performance NCORPs that have competitive, peer-reviewed grant funding to cover their participation in trials. Pediatric sites have a similar "Workload Model" within the pediatric NCTN group.

A "Medicare Coverage Analysis" (*a review of all tests, procedures, and interventions associated with a clinical trial to determine which ones are 'billable' and which are 'not billable' to a third-party payer*) is provided on NCTN trials as a centralized resource to increase efficiency and decrease burden (financial and time) on institutions.

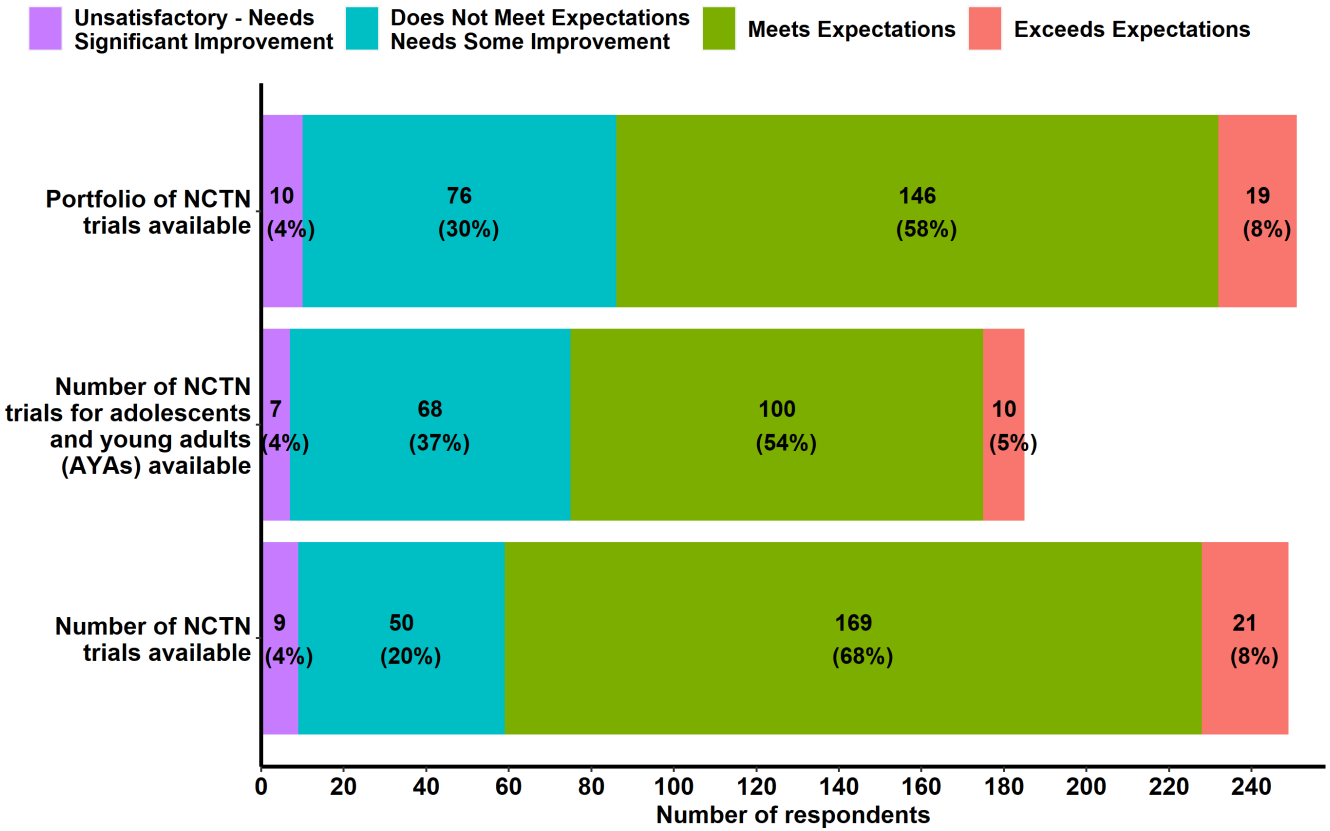
Many trials (mostly IND studies) have significant additional support from company partners, especially "registration intent" trials. Industry trials have a milestone funding approach & provide significantly higher levels of funding to sites per patient enrollment. Past analyses of Group site capitation compared to payments to sites for industry trials estimated a 2.5 to 7.5 fold discrepancy in payment amounts at that time (*IOM Report on NCI Clinical Trials Cooperative Group Program, 2010*)

Most Common Comment in Survey Overall: Funding

Themes from the qualitative comments on funding:

- **Sites increasingly forced to emphasize industry-sponsored studies over NCTN** studies, even when the science is interesting, for the practical reason that NCTN trials are under-funded
- Increasingly complex or nuanced studies in relatively infrequent patient populations often rejected by sites with limited resources to devote to NCTN studies as a result of the low per-patient reimbursement
- More funding is needed. **Even with centralized support for data & regulatory aspects, sites are less willing to consider or participate in NCTN studies b/c they have to cover the financial deficit** incurred for screening, enrollment, management & follow-up

Overall, how satisfied are you with the following aspects of the NCTN menu of trials ?



Suggestions for NCTN Trial Portfolio (1)

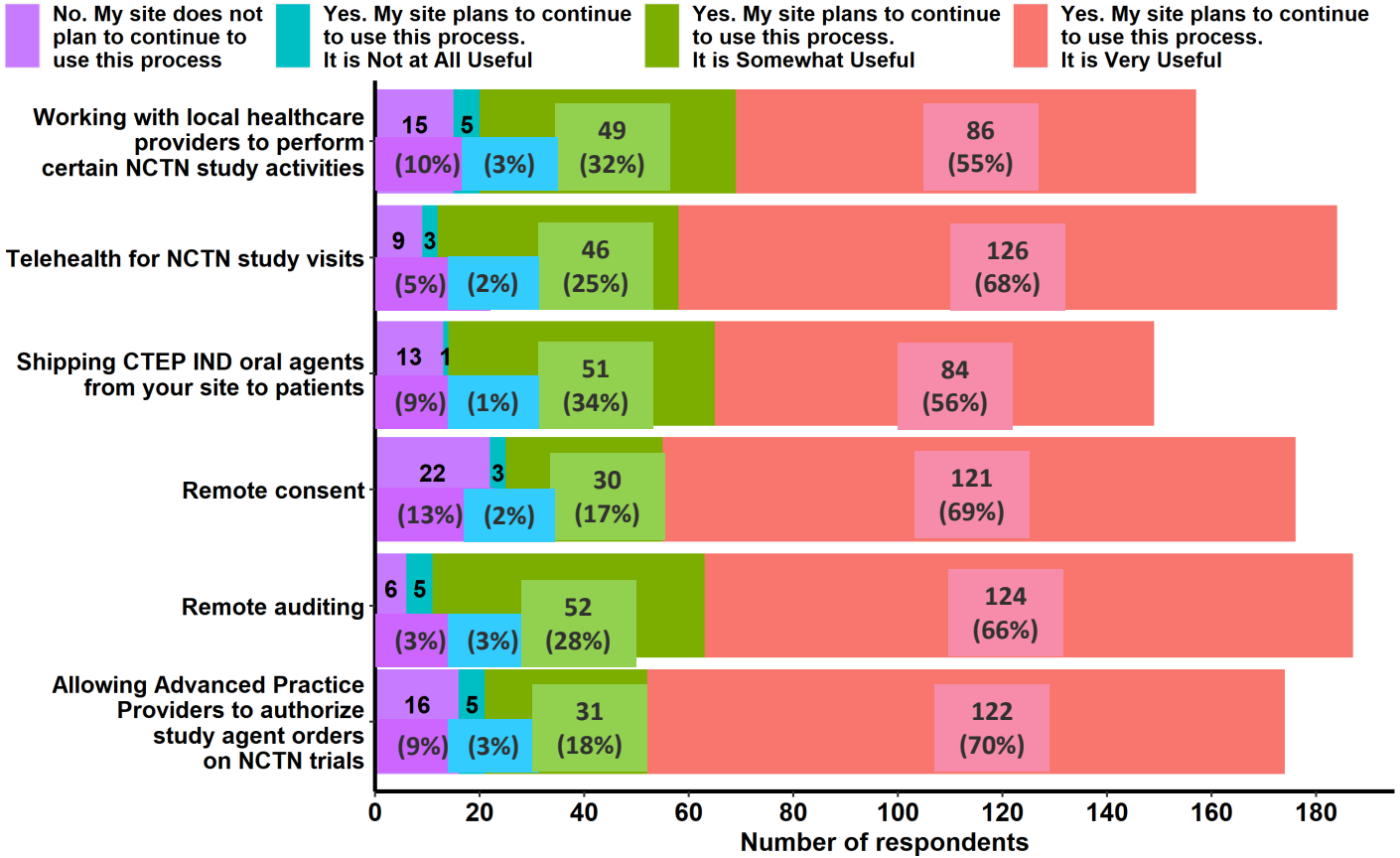
- **Continued interest in more trials for common / early-stage disease areas:**
  - Innovative science & new therapies are important; however, **there are relatively simple questions about various regimens that need to be answered that could affect standard of care that no one else will address including industry**
  - **Concern about trials for rare populations at sites that only see one of the requisite patients once every 2-3 years** – one cannot expect these sites to invest in opening & maintaining a study that burdens staff with screening for patients who rarely qualify
  - A single staff person cannot efficiently screen for 20 or 30 different studies (assuming the research staff has several different CRAs).
  - Smaller community sites do better with larger Phase 2 or Phase 3 studies with reasonable sample sizes

Suggestions for NCTN Trial Portfolio (2)

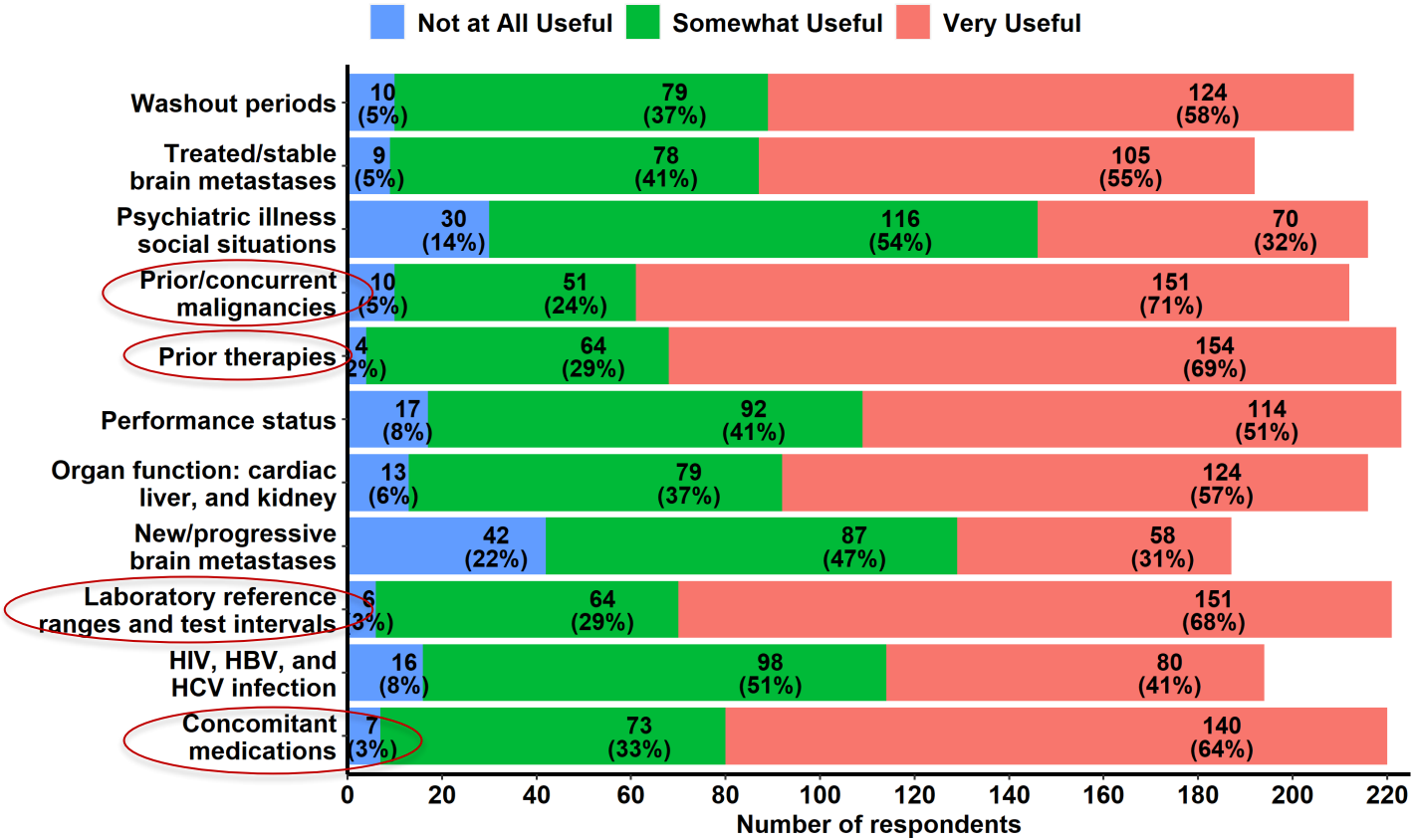
- **Differing opinions on need for more early-phase or late phase trials:**
  - NCTN was cited as allowing investigators to conduct potentially practice-altering trials that pharma companies are less incentivized to conduct
  - **Support for preserving such precious infrastructure, expertise, & resources for late-phase trials t**hat will most likely have a real impact in the field
  - **More willingness to allow signal seeking trials** (rather than focus on practice-changing trials) that are otherwise scientifically meritorious to utilize the NCTN network of sites
  - Pilot/small studies are critically important to develop the data needed for larger studies

"Manage the NCTN portfolio to assure there is a balance between large simple trials and more complex trials."

For each of the following new processes implemented during COVID-19 pandemic, does your site plan to continue to use the new process?



Which of the following categories of broadened eligibility criteria do you think will have the greatest impact?



Feedback on New COVID-19 Processes & Broadening Eligibility: Maintain and Expand

- "All of these processes above were very helpful and continue to be so, especially for patients who live a distance away. These programs allow for enrollment of more diverse patient populations."

- "Continued expansion of telehealth and remote study procedures/consent/etc. is hugely impactful in reducing the barriers to clinical trial participation."

General Takeaway: Many Positive Experiences

- “Overall, it is an outstanding system that benefits millions of people in the U.S. and worldwide, and [it] is a 'bargain' compared with industry clinical trials. There is a great need for increased funding both to the Group headquarters and to the sites enrolling and retaining patients.”

- “Overall, I am extremely grateful for the opportunity I have received in the NCTN and have learned so much from my colleagues. I have now worked to 'pay it forward' and am mentoring several colleagues through the process. … Again, I cannot thank the NCTN enough for all I have learned through this process!”

- “Overall, the NCTN has delivered what it had promised to do.”

Summary:
Responses on Concerns & Suggestions for Improvement

- **Concern with funding for all elements of the studies.** Increase funding to support increased workload of complex trials (staffing) & support enrollment and retention of underserved populations - *Need to achieve balance between funding and the burden/requirements to conduct a particular study*
- **More standardization/consistency/same expectations/common guidelines** – protocol writing, forms in RAVE, data reporting, auditing, and policies & procedures ("simplify trials") along with transparency/efficiency of review processes
- **Foster collaboration;** More intergroup/trans-NCTN meetings
- **Enhance recognition:** authorship/Joint leadership/Junior PIs
- **More timely and efficient activation of trials**
- **Continue changes implemented ~ pandemic,** more flexibility/decentralized trial activities

NCI Strategic Vision for Clinical Trials (2030 & Beyond)

NCI CTAC Strategic Planning Working Groups addressing area recommendations
CTEP working with Groups/CRAs to identify/simplify infrastructure & processes

Develop **flexible**, **faster**, **simpler**, **less expensive**, **high-impact** clinical trials that seamlessly integrate with clinical practice

- Streamline processes for trial design and execution
- Focus on essential endpoints
- Decrease regulatory hurdles and broaden trial access
- Increase efficiency of data collection

Areas for Improvement:
How Can We Continue to Improve Satisfaction?
How Do We Manage the Critical Funding Concerns?

- **In many cases, the qualitative feedback received through the survey is reflective of the NCTN's progress:**
  - Sites are enrolling to trials from multiple groups and now these sites have suggestions for how to improve this experience
  - Instead of seeking significant changes to the overarching NCTN program, respondents requested more information, guidance, & opportunities to succeed within the program
  - Many respondents suggested there should be, and there is a need for, even greater communication & opportunities for meetings across Groups