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Running Head

Pandemic impact on research involvement

Title

Stakeholder Perspectives on Engaging with Cerebral Palsy Research Studies Following Onset of COVID-19 in the United States

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Conflicts of Interest

None

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Highlights

- Participation readiness does not depend on age, CP type, or COVID-19 burden.
- During COVID-19, adults with CP are more willing to participate in research.
- Willingness to participate is influenced by whether study offers direct benefit.

ABSTRACT

Objective: To investigate the effect of the COVID-19 pandemic on perspectives towards participation in cerebral palsy (CP) research.

Design: An online survey with questions relating to the comfort levels of research participation was filled out by people who had CP or had a child with CP.

Setting: The online survey was administered through Research Electronic Data Capture (REDCap) platform.

Participants: 233 individuals with CP (42.5%) or with a child with CP (57.1%) consented and at least partially completed the online survey (n=210 complete; n=23 partially complete). All participants resided in the United States.

Interventions: Not applicable.

Main Outcome Measures: Readiness to participate was analyzed in the context of the timepoint for research participation (TRP) during COVID-19 and whether or not the study offered direct benefits to participants.

Results: Participants were consistently willing to participate sooner in studies that offered direct benefit than in those that did not. Adults responding for themselves had sooner timepoints for studies without direct benefit compared to parents answering for a child (p=0.030). GMFCS level, but not age or CP type, impacted the timepoint for studies without direct benefit (p=0.017). Personal values influenced selected timepoint for studies without direct benefit (p=0.007), while environmental factors impacted the timepoint for studies with direct benefit (p=0.002). Local COVID-19 incidence rates were not associated with timepoints for either research type, however respondents expected precautions to be taken if they chose to participate.

Conclusion: As the pandemic evolves, researchers should consider the perspectives of potential participants as well as ethical and safety factors when re-initiating in-person CP research.

Keywords: cerebral palsy, research participation, research recruitment, COVID-19, pandemic

ABBREVIATIONS

COVID-19: Coronavirus Disease 2019 (the 2019 coronavirus global pandemic)

CP: cerebral palsy

DB: direct benefit

GMFCS: Gross Motor Function Classification System

NDB: no direct benefit

REDCap: Research Electronic Data Capture

TRP: timepoint for research participation

TRP-DB: timepoint for research participation for studies that have potential direct benefit

TRP-NDB: timepoint for research participation for studies that have no direct benefit

MAIN TEXT

Research studies are the primary mechanism by which clinicians and scientists improve understanding of pathophysiology and treatment options for cerebral palsy (CP), a group of movement disorders caused by injury or disruption to the developing brain.[1] An estimated 60-80% of rehabilitation studies in the United States do not meet their expected sample size,[2] and studies that focus on pediatric populations, including CP, are prone to difficulties in recruiting the number of participants required for scientific validity.[3,4]

The coronavirus disease (COVID-19) global pandemic has resulted in widespread stay at home orders and social distancing, which has impacted the ability to carry out in-person research studies. Some regions began to re-open businesses and schools by summer of 2020, but there is not consensus on how to ethically and safely re-initiate human subject research. Scientists must consider visit-related factors, policy-related factors, research facility preparedness, and research participant perspectives[5] in evaluating the overall risk of resuming human subject research. The current study investigates the personal and environmental factors that influence

comfort levels of participant stakeholders for participating in CP research during the COVID-19 pandemic.

Methods

An online survey was developed by the study team with review by 6 stakeholders who had CP or a child with CP. The survey was available online between May 6 and July 7, 2020 and disseminated through the Research Electronic Data Capture (REDCap)[6,7] platform. Informed consent was collected from all participants. The survey consisted of up to 60 questions, with 14 specifically related to comfort with in-person research study participation during the COVID-19 pandemic (Figure S1). This study was approved by Northwestern University's Institutional Review Board.

Recruitment

Participants had to reside in the United States and be *either* (1) a parent or legal guardian of a minor with CP or (2) an adult with CP. Participants were recruited directly via email if they had previously participated in pediatric studies at Northwestern University or consented to be contacted through the web-based recruitment tool ResearchMatch.org.[8] Eligible members of the Cerebral Palsy Research Registry[9] were sent a recruitment notification and clinical partners were encouraged to share the study with eligible patients. Finally, social media sites (Facebook, Twitter, Instagram) were used to share the survey link.

Data Analysis

All statistical analyses were conducted using SPSS software (version 26, SPSS Inc, Chicago, IL) with $p < 0.05$ considered statistically significant. Descriptive analysis was completed for age, sex, ethnicity, race, CP diagnosis, and Gross Motor Function Classification System (GMFCS) level. Survey data was analyzed to address the following research questions:

Q1: How soon are potential participants willing to participate in research?

Participants were asked to identify the earliest milestone at which they would be comfortable to join a research study. They were asked to separately answer for studies with potential for Direct Benefit (DB; i.e. clinical trials of interventional physical and occupational therapy studies, drug and treatment efficacy, intensive training) and with No Direct Benefit (NDB; i.e. studies aiming to understand basic scientific and biomechanical background of CP). The milestones presented to respondents included: (a) now, (b) following lifting of local stay-at-home orders, (c) following widespread testing for COVID-19, (d) following availability of COVID-19 vaccination, and (e) not in the foreseeable future. Because milestones are ordered chronologically, timepoint for research participation (TRP) was coded for analysis with earliest selected timepoint for a given activity, with the assumption that the respondent would also be willing to participate for the later timepoints. Analysis focused on timepoints for studies that have potential direct benefit (TRP-DB) and studies that have no direct benefit (TRP-NDB).

Q2: How does participating in research activities compare to other activities?

Participants were asked the earliest milestone (as in Q1) they would engage in the following activities: 1) personal care appointments, 2) social or recreational activities, 3) routine medical appointments, and 4) medical appointments for a new concern. Chi-square tests were performed to analyze whether there was association between the TRP-DB and TRP-NDB and the timepoints they were comfortable participating in non-research activities. Spearman correlations were observed to determine the strengths of association.

Q3: Are demographic characteristics of the potential participant associated with timepoint for research participation?

Separate Kruskal-Wallis tests with TRP-DB and TRP-NDB as dependent variables and age, GMFCS level, or CP diagnosis as independent variables were performed. For significant main effects, pairwise comparisons were performed with Bonferroni correction for multiple tests.

Q4: Which personal values are associated with timepoint for research participation?

Personal values included self-rated value placed on CP research overall and participation in CP research. Linear regression was performed with each of these values as predictors, and TRP-DB and TRP-NDB as the outputs.

Q5: How are environmental factors, including the overall COVID-19 risk, associated with choices about engaging in research activities?

The risk of COVID-19 was represented by the incidence rate (cases per 100,000 persons) for each respondent's state on the date of survey completion, which was obtained from the COVID-

19 Data Repository by the Center for Systems Science and Engineering at Johns Hopkins University.[10] This COVID-19 risk metric, along with preferred location of research participation (regardless of COVID-19 consideration) and transportation typically used for medical appointments, was used in linear regression models to determine whether environmental factors could predict when individuals were willing to participate in in-person research studies (TRP-DB and TRP-NDB).

Q6: What are common responses about participant decision making during COVID-19?

Open-ended questions about the impact of COVID-19 on research participation decisions were categorized first by whether it had an impact (yes, no, or unsure), and further organized by stated reason(s) for response.

Results

Participants

In total, 241 individuals were consented and 233 submitted complete (n=210) or partially complete (n=23) surveys. The final sample represents a 10.3% response rate of those directly contacted via email, ResearchMatch.org, and the Cerebral Palsy Research Registry (n=2266). Study sample characteristics are shown in Table 1. In comparison to the US 2010 Census data, the sample is broadly representative of the national population in terms of sex, ethnicity, and racial composition. Notably, the sample included more respondents who were parents of

children with CP (57.1%) than adults with CP (42.5%), as opposed to the national population which consists of 24% minors and 76% adults.[11] When results are similar among the caregivers of a child and adults with CP, the term respondent is used to generalize to both; when the results or trends are different, caregiver and adult responses are reported independently.

Participants came from 33 states, as illustrated in Figure S2. Over half the respondents reside in Illinois (54.5%). The next three most represented states were Indiana (4.72%), California (3.86%), and New York (3.43%). The incidence rates of COVID-19 across the country for the dates of the survey are represented in maps shown in Figure S2. The total incidence rate in the US increased from 18,110 to 41,637 cases per 100,000 persons over the duration of the survey.

Timepoints for research participation (Q1)

As shown in Figure 1, more respondents indicated willingness to participate in DB studies compared to NDB at each of the timepoints. Over a fifth (23.1%) of the respondents indicated TRP at survey completion ('now') in an NDB study, while 39.1% would participate 'now' in a DB study. For both study types, the percentage of respondents willing to participate has the steepest rise between 'now' and the 'lifting of local stay at home orders'. A DB study has the smallest change between 'widespread testing' and 'availability of a vaccination' (11.2%), while an NDB study has the smallest change between lifting of stay at home orders and widespread testing (20.3%). Frequencies of responses for each TRP can be found in Table S3.

Perceptions of research studies compared to other appointments (Q2)

As shown in Figure 1, at the time of survey completion, the majority of respondents were comfortable going to a medical appointment for a new concern (61%) while few were willing to participate in a social or recreational activity (9%). Significant associations were found for all combinations tested ($p < 0.001$). Research studies with DB were most closely associated with a routine medical appointment ($r_s = 0.564$, $p < 0.001$), while NDB studies had the highest correlation with a social or recreational activity ($r_s = 0.600$, $p < 0.001$). Both types of research studies were least correlated with a medical appointment for a new concern (DB: $r_s = 0.484$, $p < 0.001$; NDB: $r_s = 0.384$, $p < 0.001$) (Table 2).

Timepoint for research participation relationship to demographics (Q3)

Whether the survey respondent was answering for themselves (as an adult with CP) or for their child did not impact the TRP-DB ($H(1) = 0.008$, $p = 0.930$), but did significantly impact the TRP-NDB ($H(1) = 4.708$, $p = 0.030$), where adults with CP had an earlier TRP-NDB than parent respondents (Figure 2A). At time of survey completion, 15.7% more adults than parents responded 'now' representing the greatest difference between groups. Group differences reduced chronologically with almost the same percentages willing to participate 'following the availability of vaccination' (adults: 92.6%, parents: 92.3%) for NDB studies.

Across all age groups, TRP was on average sooner for DB compared to NDB (Figure 2B). Adults with CP in the 31-50 year age group reported the earliest TRP; caregivers of children 2-3

years reported the earliest TRP. No significant differences were found between the age groups in TRP-DB ($H(6) = 6.360$, $p = 0.384$) nor TRP-NDB ($H(6) = 9.856$, $p = 0.131$).

For both types of studies, individuals and caregivers of children in GMFCS Level IV and Level V were the least willing to participate at earlier timepoints (Figure 2C). On average, individuals or caregivers of children in GMFCS Level III were the most willing to participate across all TRP milestones. While there were no significant differences between GMFCS levels in TRP-DB ($H(4) = 3.917$, $p = 0.417$), there were significant differences with TRP-NDB ($H(4) = 12.008$, $p = 0.017$). Specifically, there were significant differences in the TRP-NDB between Level III and Level IV ($t = -45.172$, $p = 0.024$) and between Level III and Level V ($t = -45.486$, $p = 0.035$). To account for the uneven sample sizes across the GMFCS levels and confirm the significant differences identified by the initial analysis, a post-hoc Monte Carlo simulation was run with 100 iterations, with 30 subjects with Level I and Level II randomly chosen for inclusion in analysis with Levels III, IV, and V. Across the 100 iterations, there was no significant relationship between GMFCS level and TRP-DB, but there remained a significant relationship between GMFCS level and TRP-NDB. Furthermore, of the iterations showing significant group-wise differences in TRP-NDB, 4% showed differences between Level II and Level III (average $t = 16.625$, average $p = 0.0335$), 100% showed differences between Level III and Level IV (average $t = -29.0386$, average $p = 0.0259$), and 96% showed differences between Level III and Level V (average $t = -28.8884$, average $p = 0.0355$).

No significant differences were found between the CP types in TRP-DB ($H(3) = 1.186$, $p = 0.756$) nor TRP-NDB ($H(3) = 4.579$, $p = 0.205$). On average, there are more adults or caregivers of children with hemiplegia and diplegia willing to participate at sooner timepoints than those

with quadriplegia, while the respondents who reported “Other” for CP diagnosis were the least willing to participate (Figure 2D).

Personal predictors of timepoint for research participation (Q4)

The mean for self-rated value placed on CP research (out of 100) was 94.3 (SD=9.05) and value placed on their own participation in CP research was 88.6 (SD=16.6). The regression model for TRP-NDB was significant (Table 3) where both value of research and value of participation in research were significant predictors. The TRP-NDB was later as value placed on research increased (p = 0.037) and sooner as value placed on participation increased (p = 0.002). The model for TRP-DB was not significant (Table 3).

Environmental predictors of timepoint for research participation (Q5)

Prior to COVID-19, 69.5% of respondents would have participated in research in a research lab and 43.3% of respondents would have participated in a school. These two locations were significant predictors (research lab: p=0.001; school: p=0.022) for a sooner timepoint in the TRP-DB regression model with research location (Table 3). The regression model for TRP-NDB was not significant (Table 3).

Qualitative responses to the impact of COVID-19 on research participation (Q6)

Seventy two percent of survey participants (n=169) answered about whether COVID-19 impacted their feelings on research participation. Participant responses reflected a range in whether COVID-19 impacted feelings on research participation and many provided additional reasons for their perceptions (Figure 3). The most common reasons included if proper precautions were taken, travel distance to and location of the study site, or if the participant or a family member was immunocompromised. Selected quotes can be found in Table S4.

Discussion

This study explored the comfort level of participating in research by individuals with CP during the COVID-19 pandemic by analyzing willingness to participate in two key categories of in-person research studies: *studies that offer potential direct benefit* (DB) and *studies that do not offer direct benefit* (NDB). The findings revealed a number of important considerations for researchers as they plan research during COVID-19.

The majority of respondents were willing to attend either an acute or routine medical appointment in the near future, but few were comfortable with casual, non-essential outings, such as personal care or social activities, potentially due to immunocompromised family members or anxiety about the pandemic. Research participation is perceived as less urgent than medical needs, but is more important than casual outings, with DB studies similar to a routine medical visit and NDB studies similar to a social activity. While specific dates for these milestones depend on local regulations and will vary by location, these results illustrate a

general timeline that can be followed by researchers when preparing for engagement in research.

While COVID-19 is rapidly evolving, it has been shown that older adults with the illness have higher mortality rates (median age of death greater than 65 years),[12] and individuals of any age with underlying medical conditions are more susceptible to the disease and have worse prognosis.[13] Despite elevated risk, age was not a significant factor in TRP, although a related factor of the person completing the survey (adult with CP or parent/guardian of a minor with CP) was significant. Compared to adults answering for themselves, parents were less comfortable with their children participating. This may be related to the total number of individuals from a family that need to be engaged, a parental drive to be protective, or a fear of their own child being a “guinea pig” for clinical testing.[14]

GMFCS level did have a significant impact on the willingness to participate in an NDB study, where Level IV or Level V groups who are more likely to have severe comorbidities[15,16] were the most conservative in their approach. In contrast, GMFCS level did not have an impact on TRP-DB, and the type of CP diagnosis did not impact TRP in either type of study. Post-hoc Monte-Carlo tests revealed that results were robust to sample size differences.

The more that a respondent valued their own participation in research, the sooner they were likely to be willing to participate in NDB studies. Conversely, value of research in general (disregarding their own involvement) actually predicted a later TRP. Although these relationships were significant, the notable finding is that though research and participation are

highly valued by respondents, risk of COVID-19 exposure may impact personal decision on when to participate.

Environmental factors related to pre-COVID-19 life appeared to have a small influence on an individual's TRP-DB but not TRP-NDB. Particularly, selection of a research lab or school as a potential study location indicated that respondents would participate sooner in studies that offer direct benefit. This could be related to perceived structure of these two locations instilling confidence in the quality of research, and may extend to an expectation of precautions and safety measures against COVID-19,[17,18] although this would require further investigation. Although few respondents (32.6%) considered outdoor recreational spaces for research participation prior to COVID-19, outside may be a reasonable solution in some study locations during the pandemic[19] for safe in-person participation.

Surprisingly, the local burden of COVID-19, represented by the local COVID-19 incidence rate on the day the respondent took the survey, did not have a significant impact on the TRP for either type of research study. We did not specifically gauge respondents' knowledge of their community's burden at the time of the survey. Recent surveys revealed variable understanding of the mode of transmission and symptoms of COVID-19[20–22] with considerable inaccurate beliefs regarding origination, transmission, and prevention of COVID-19,[21] including among those with chronic conditions.[22] Although misunderstanding of COVID-19 information could skew reactions, there are also local burdens not directly captured by incident rate or other quantitative values that may influence responses and may be reflected in open-ended answers.

Study Limitations

COVID-19 incidence rates used were those recorded at the state level, however finer precision at the county- or zip code-level may yield a tighter coupling with local attitudes especially in metropolitan areas. Additionally, the majority of participants resided in Illinois and only 33 states were represented, introducing a potential geographical bias in the results. Demographically, there is a slight underrepresentation of minorities (Hispanic/Latino ethnicities and non-White races) and no data indicating socio-economic status of respondents, both of which are factors that are significantly correlated with COVID-19 burden.[23] Finally, respondents were asked to answer some questions as they would have prior to COVID-19, which may have been impacted by recall bias.

Conclusion

There is limited guidance on how human research, particularly in pediatric and at-risk populations, should be safely carried out during COVID-19. The current study provides insight into the perceptions of individuals with CP or their caregiver when considering engaging with research. Results from this study could also serve as the basis for further exploration about how readiness for participation may be improved in collaboration with potential participants for a specific study. The relatively large numbers of respondents willing to engage in research during the COVID-19 pandemic demonstrates the importance of partnership for new discovery in CP. It is therefore the responsibility of investigators to reach out to potential participants or participant representatives to implement research in a way that is both respectful of necessary scientific rigor and responsible to the public health crisis.

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FIGURE LEGENDS

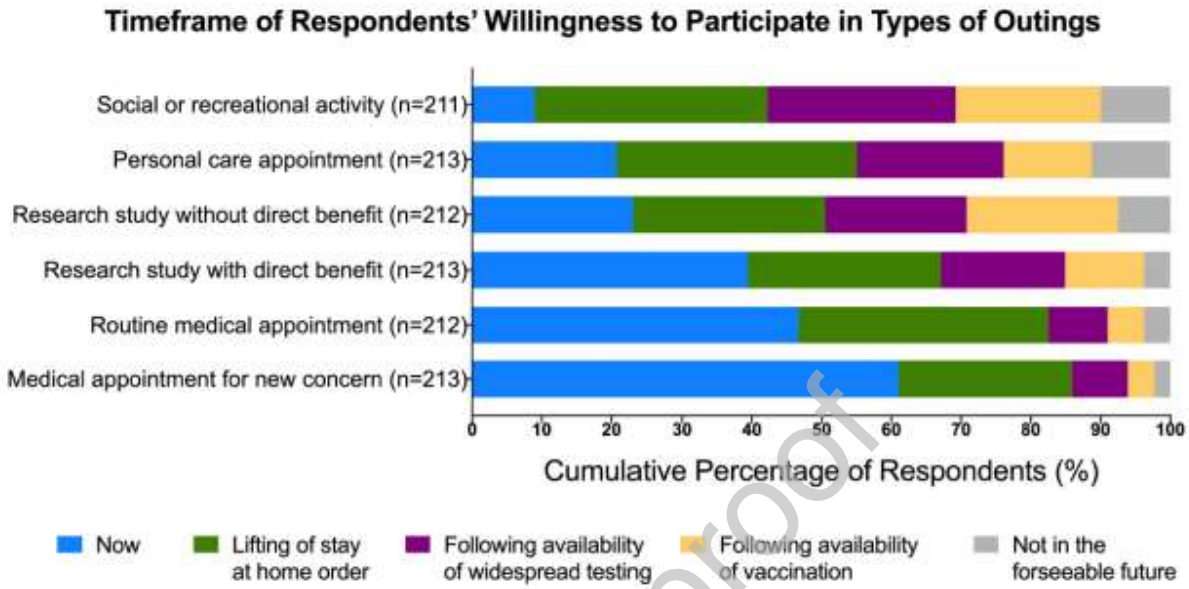

Figure 1. The number of respondents willing to partake or have their child partake in each of six types of outings – social or recreational activity, personal care appointment, research study without direct benefit, research study with direct benefit, routine medical appointment, or a medical appointment for a new concern – at each of the COVID-19 related milestones. The cumulative percentage of respondents is shown, such that the number of respondents that was ready at each timepoint was added with the number of respondents that stated they were ready to participate at earlier timepoints.

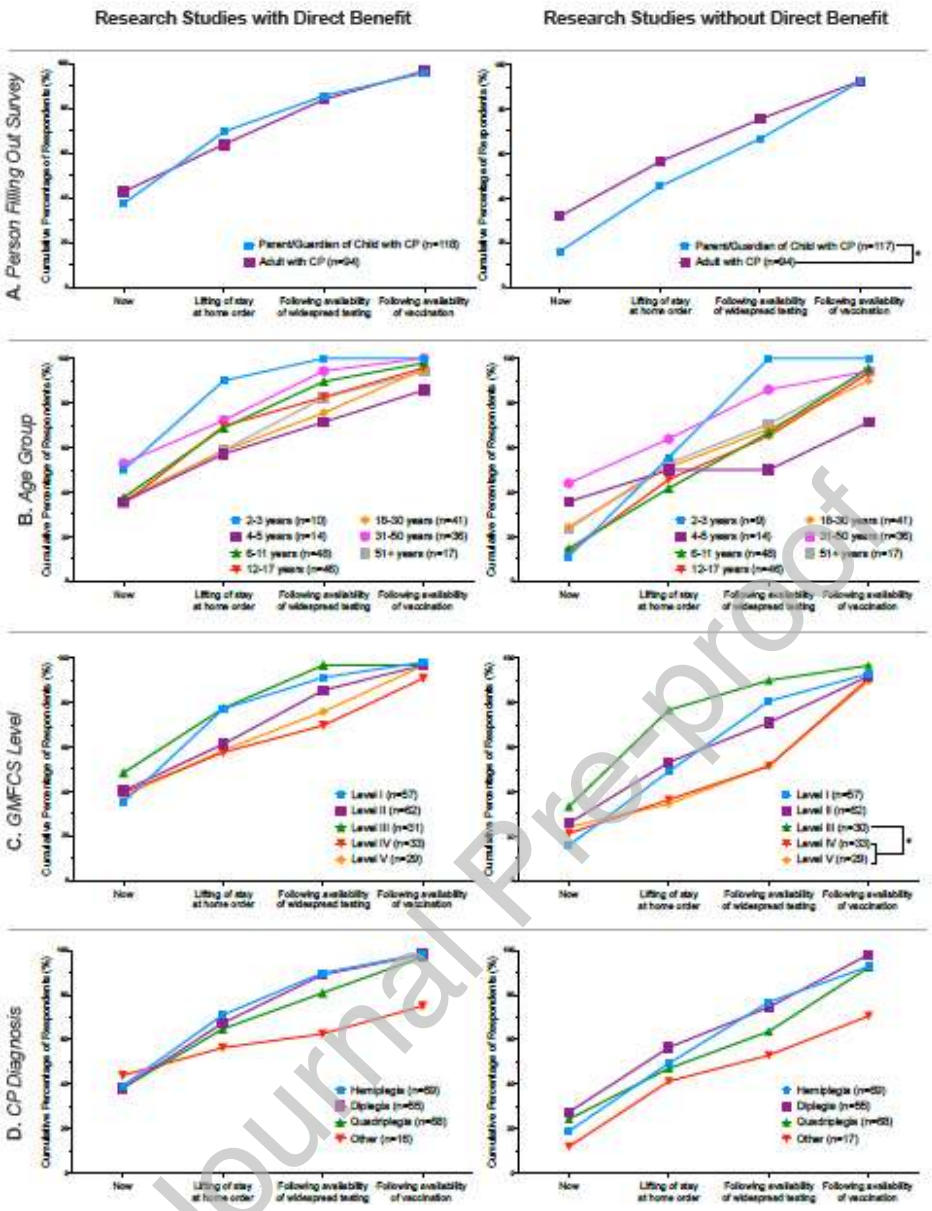

Figure 2. Cumulative number of respondents willing to participate in research studies that offer direct benefit (*left*) and studies that do not offer direct benefit (*right*), separated by **(A)** minor or adult status of respondent, **(B)** age group, **(C)** GMFCS level, and **(D)** type of CP diagnosis. An asterisk (*) indicates significance at $p < 0.05$.

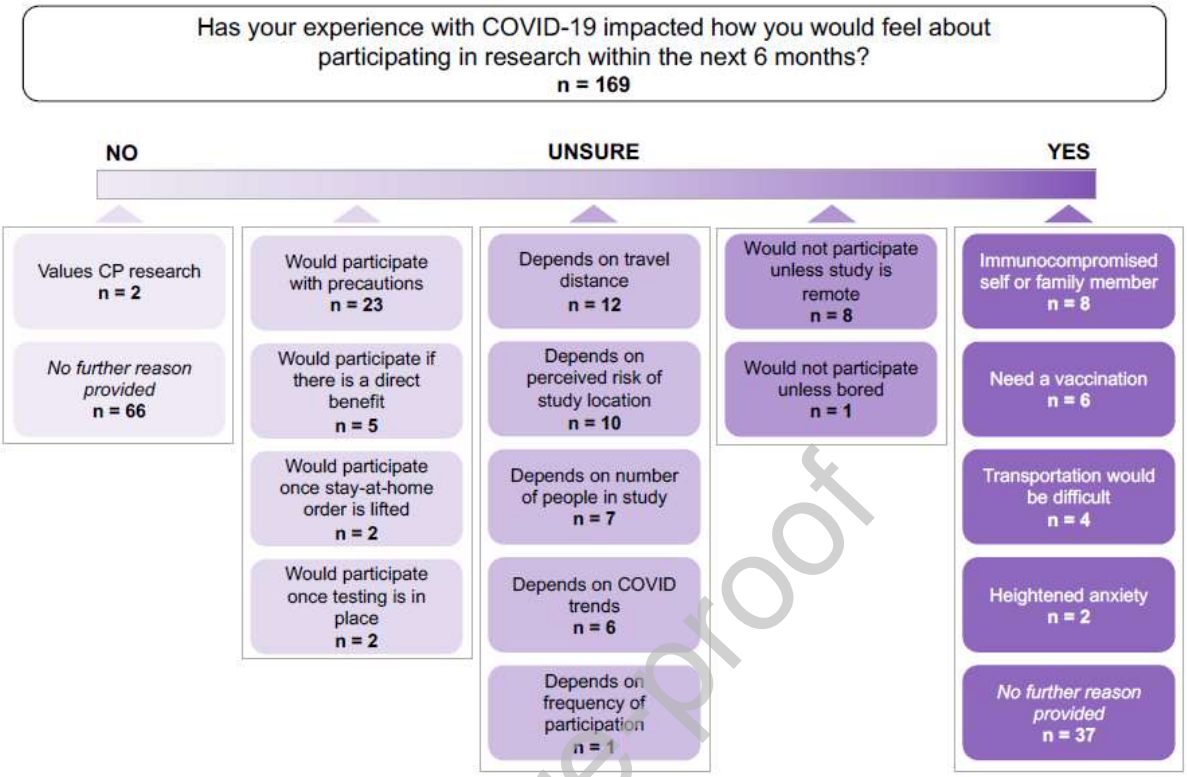

Figure 3. Spectrum showing the range of qualitative responses to the impact (or lack thereof) that COVID-19 had on participants' feelings towards research participation (n=169, 72.5% of total survey respondents). Using keywords, responses were first categorized broadly into "yes, research participation was impacted", "no, research participation was not impacted", and "unsure if research participation was impacted". Then, the "yes" and "no" responses were subcategorized into "strong yes", "strong no", "leaning yes" and "leaning no". The "leaning yes" and "leaning no" categories indicated that the respondent's feelings could be swayed by additional factors, which are listed. Some of the "strong yes" and "strong no" responses provided reasoning, which are also shown. Many responses fell into multiple categories. The ends of the spectrum represent "strong yes" and "strong no" responses while the center of the spectrum represents "unsure responses". The proximity of responses to either end of the spectrum represents the strength of the "yes" or "no" response.

TABLE LEGENDS

Table 1. Characteristics of study sample. Survey percentages are compared to national census and previously published reports on distribution of CP. National census and CP population percentages taken from: (a) Age and Sex Composition, 2010 Census Briefs[23]; (b) Overview of Race and Hispanic Origin, 2010 Census Briefs[24]; (c) Using the Gross Motor Function Classification System to describe patterns of motor severity in cerebral palsy[25]; (d) Prevalence of Cerebral Palsy in 8-Year-Old Children in Three Areas of the United States in 2002: A Multisite Collaboration.[26]

Characteristics	Survey Sample		Population (%)[a,b,c,d]
	n	%	
Total Number of Respondents	233	100	
Age group (years)[a]			
0-1	2	0.9	
2-3	10	4.3	
4-5	14	6.0	
6-11	53	22.7	
12-17	54	23.2	
Total: Under 18	133	57.1	24.0
18-30	45	19.3	
31-50	36	15.5	
51+	18	7.7	
Total: Over 18	99	42.5	76.0
Unknown/Not reported	1	0.4	
Sex assigned at birth[a]			
Female	120	51.5	50.8
Male	112	48.1	49.2
Unknown/Not Reported	1	0.4	

Ethnicity[b]			
Hispanic or Latino	23	9.9	16.3
Not Hispanic or Latino	204	87.6	83.7
Unknown/Not Reported	6	2.6	
Race[b]			
American Indian or Alaska Native	2	0.9	0.9
Asian	9	3.9	4.8
Black or African American	24	10.3	12.6
Native Hawaiian or Other Pacific Islander	1	0.4	0.2
White	175	75.1	72.4
Two or More Races	6	2.6	2.9
Unknown/Not Reported	16	6.8	
Gross Motor Function Classification System (GMFCS)[c]			
Level I	60	25.8	34.2
Level II	65	27.9	25.6
Level III	33	14.2	11.5
Level IV	37	15.9	13.7
Level V	35	15.0	15.6
Unknown/Not Reported	3	1.3	
Cerebral Palsy diagnosis[d]			
Hemiplegia	72	30.9	22.6
Diplegia	60	25.8	22.4
Quadriplegia	76	32.6	25.0
Other	19	8.2	30
Unknown/Not Reported	6	2.6	

Table 2. Ranking of associations between direct benefit and indirect benefit research studies with the other types of outings. Associations were ranked by Spearman correlation values, with a higher Spearman value indicating a stronger association and a lower Spearman value indicating a weaker association. For each correlation, Spearman values are reported with the number of valid samples n, and Chi-square values are reported with the degrees of freedom df. The p-values for Spearman and Chi-square tests for all correlations were found to be less than 0.001.

Research Study with Direct Benefit			**Research Study without Direct Benefit**		
	Spearman (n)	Chi-Square (df)		Spearman (n)	Chi-Square (df)
Routine Medical Appointment	0.564 (210)	213.287 (16)	*Social or Recreational Activity*	0.600 (210)	204.413 (16)
Personal Care Appointment	0.554 (212)	165.307 (16)	*Personal Care Appointment*	0.543 (212)	181.356 (16)
Social or Recreational Activity	0.522 (210)	160.841 (16)	*Routine Medical Appointment*	0.476 (210)	140.239 (16)
Medical Appointment for New Concern	0.484 (211)	246.939 (16)	*Medical Appointment for New Concern*	0.384 (210)	91.778 (16)

Table 3. Linear regression parameters of the impact of personal predictors and environmental predictors on the readiness to return to research studies with and without direct benefit. Whole model output and significance values are reported, as are coefficients and significance of individual predictors. Beta values refer to the standardized coefficients resulting from the regression. An asterisk (*) indicates significance at p < 0.05.

Personal Predictors				
	Research Study with Direct Benefit		**Research Study without Direct Benefit**	
	$F(2,201) = 0.269$, $p = 0.764$		$F(2,200) = 5.117$, $p = 0.007$*	
	Beta	*p-value*	*Beta*	*p-value*
Value placed on				
Research	0.049	0.558	0.172	0.037*
Participation	-0.057	0.493	-0.259	0.002*
Environmental Predictors				

	Research Study with Direct Benefit $F(13,191) = 2.692$, $p = 0.002$*		**Research Study without Direct Benefit** $F(13,190) = 1.453$, $p = 0.139$	
	Beta	*p-value*	*Beta*	*p-value*
COVID-19 Incidence	-0.049	0.486	-0.077	0.296
Location				
Clinic/hospital, already receiving services	0.048	0.488	0.033	0.643
Clinic/hospital, not already receiving services	-0.111	0.137	-0.127	0.104
Park/community center	0.017	0.829	0.031	0.698
Research Lab	-0.267	0.001*	-0.159	0.046*
School	-0.178	0.022*	-0.128	0.112
Home	0.015	0.832	-0.031	0.668
Other Location	-0.050	0.463	-0.003	0.961
Transportation				
Drive self	0.137	0.161	0.175	0.087
Family member drives	0.070	0.401	0.096	0.272
Public transportation	0.076	0.384	0.036	0.694
Car service	1.045	0.297	0.091	0.287
Other transportation	0.057	0.452	0.053	0.502