

Additional File 3. Results of the 2017 SMA Clinical Trial Site Survey

Background and Purpose of Survey

During August – September 2017, Cure SMA surveyed clinical trial sites with experience conducting clinical trials in SMA to (a) understand sites' capacity for future clinical trials in SMA, (b) identify factors that may limit site trial capacity and/or readiness, and (c) identify opportunities to increase capacity. All sites in the United States with experience conducting clinical trials (N=21) were contacted. Nineteen (n=19) sites completed the survey; one (1) site did not respond to the survey requests, and one (1) site declined to complete the survey. Following initial review of survey responses for completeness, a subset of sites was contacted to address outstanding questions about their submissions. Survey findings are presented here and have not been published prior to this.

Summary of Findings

On the whole, sites felt more strongly about the factors that enabled them to run trials than factors limiting their capacity. Key observations on specific factors are discussed below.

Patient Populations

The participation in research generally increased proportionally with total population size, although some sites had comparatively high levels of participation, while others were below average. Both the linear trend and numerical average suggest that clinical sites enroll on average approximately 20-25% of their total clinic and research population in clinical trials.

Studies Underway at Sites

There were large variations in the number of studies underway at different sites. There was only a weak correlation between the number of studies and the size of the SMA research population at individual sites and no clear relationship between the number of trials at a site and the percentage of the SMA patient population participating in research. Sites were not asked to list each of the trials underway to minimize burden; however we recognize that some sites only included trials underway while others included prospective trials (with IRB approval but no recruited patients), as part of their overall numbers.

Site Staff

There was large variability in staffing across sites, and no clear trends were identified when comparing the numbers of the key staff to the sizes of research population at SMA sites or the number of SMA studies underway.

Site Capacity

Notably, all but one of the survey respondents indicated that their sites have capacity to conduct additional SMA trials at this time.

Factors that Have Enabled Sites to Successfully Run Trials

Sites were asked to rank the significance of enabling factors including (a) clinical staff bandwidth, (b) staff and site coordination, (c) performance of the clinical trials coordinator, (d) staff expertise in SMA, and (e) site infrastructure. Staff bandwidth, coordination, and

performance of coordinators were all endorsed as extremely important to successful trial management, but no one factor clearly stood out as most important to successfully running trials.

Factors Preventing Sites from Taking on Additional Trials

Sites were asked to rank the significance of two categories of factors related to (a) the site and its staff and (b) patients. Potential site and staff limiting factors covered by the survey were clinical staff bandwidth, trial staff bandwidth (including bandwidth of staff with SMA experience specifically), infrastructure, and other factors. Bandwidth of clinical and trial staff emerged as most significant. However, these were only highly significant for a fraction of sites. They were not significant for about half of the sites. Bandwidth of staff with SMA expertise and limited site infrastructure did not appear to be significant factors. In terms of patient-related factors, sites were asked about patient interest, distance from sites, patient saturation due to ongoing open label extension trials, and increased numbers of patients being followed as new treatment options become available. No individual factors emerged as highly significant in limiting capacity.

Opportunities for Cure SMA & the Cure SMA Industry Collaboration to Support Sites

Sites were asked to rank a series of potential approaches to addressing capacity challenges, and to provide free text suggestions for activities Cure SMA could undertake to support sites. Items ranked by sites included increasing numbers of clinical staff, trial staff, coordinators, principal investigators, and physical therapists; PT training in outcome measures; site visits with an experienced trial coordinator to identify opportunities to improve efficiency; and increased patient interest in trials. Increasing numbers of clinical staff, trial staff, and coordinators would be most helpful to sites. PT training in outcome measures and visits from coordinators would be helpful to a handful of sites, but about half of the respondents indicated that PT training would not be helpful for their sites. In free-text responses, sites also suggested: raising awareness of trials amongst the patient community in general, raising awareness about under-utilized sites and assistance with enrollment, and grants to support expanded infrastructure and coordinators.

Application of Learnings

Learnings from this survey informed Cure SMA's plan for optimizing trial site readiness and capacity, and development of the Cure SMA Clinical Trial Readiness Program. Based on the initial findings of this survey, Cure SMA concluded that sites with experience running SMA trials may benefit most from awareness-raising communications about clinical trials generally; a subset of these sites may also benefit from resources to help coordinators optimize internal coordination and efficiency. Based on the factors respondents identified as most important to successfully running trials, Cure SMA concluded that resources likely to be of the greatest value to new SMA trial sites would include training and resources for clinical research coordinators and physical therapists, resources to support research teams' understanding of SMA and team coordination.

Results of Survey Analysis

Results of the analysis of survey data are presented below.

I. Patient Populations

The first section of the survey asked sites for information about their patient populations, including sizes of populations, participation in research, and factors driving referrals to the site.

Sizes of Sites' Patient Populations

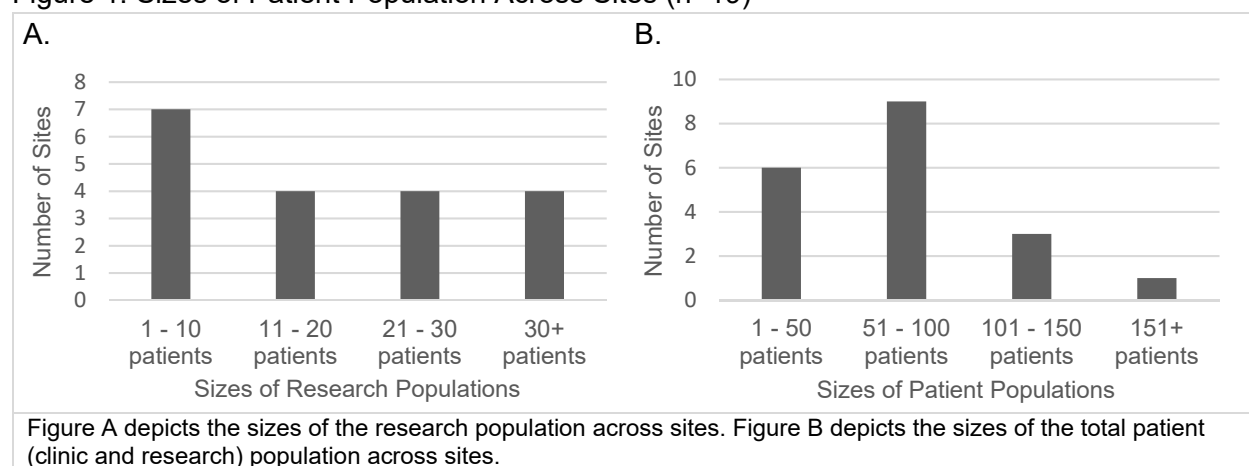
When looking at the information obtained about patient populations – presented in the tables and charts below – it is clear that there is wide variation across sites. In terms of numbers of patients seen for routine clinical care, population sizes ranged from 10 to 200 patients, with an average size of 71.8 patients. Clinical trial population sizes ranged from two to 45, with an average size of 17 patients. Total patient population sizes (including patients seen for routine care, research and care, and research only) ranged from 14 to 215 patients, with an average size of 78.3. Only one site had a population greater than 150 patients.

Table 1. Sizes of Clinic, Research, and Total Patient Populations at Sites Surveyed (n=19)

	Minimum	Maximum	Median	Mean	St Dev
# Patients Receiving Routine Care	10	200	70	71.8	44.9
# Patients Seen for Clinical Trials	2	45	15	17.4	13.0
Total # Patients Seen (Clinical and Research)	14	215	73	78.3	47.8

To better understand the distribution of total patient and research population sizes across sites, sites were grouped into the size categories below. From these distributions, it is clear that there is greater variation in the sizes of research populations across sites than in the sizes of total populations.

Figure 1. Sizes of Patient Population Across Sites (n=19)



Participation in Research

As with population sizes, there was considerable variation in the percentages of total SMA patient populations participating in research across sites. The lowest participation rate was about 5%, while one site reported that 75% of its patients were involved in research (however, this was a unit with a very specific focus, which likely resulted in a higher rate of participation than most sites would otherwise have).

To identify potential trends in terms of research participation, research populations and the percent of total patient populations participating in research were plotted against total site populations. The former plot demonstrated that participation in research generally increased proportionally with total population size, although some sites were positive outliers (with comparatively high levels of participation), while others were below average.

Table 2. % of Patient Population Participating in Research Across Sites (n=19)

	Minimum	Maximum	Mean	St Dev
% of Patient Population Participating in Research	4.8%	75.0%	23.9%	17.7%

Figure 2. Research Participation at Sites (n=19)

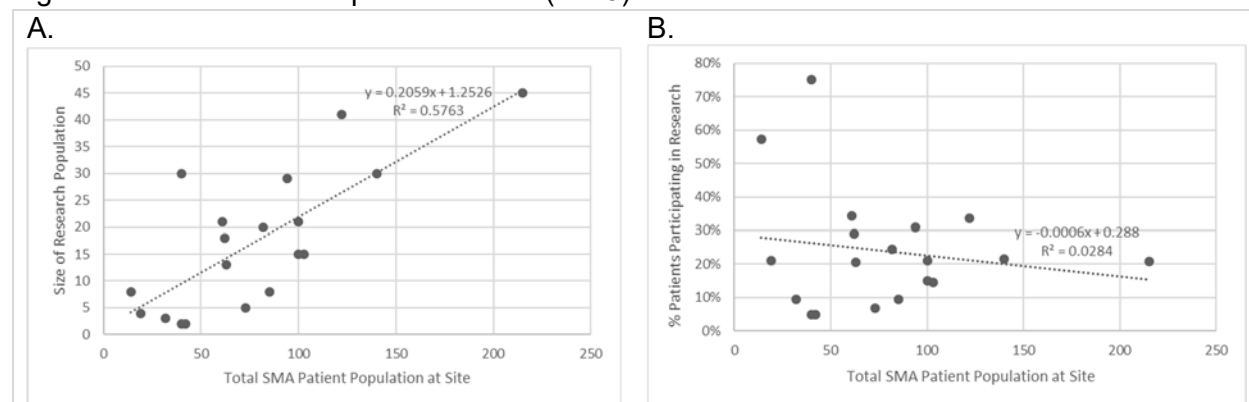


Figure A depicts the research population vs the total SMA patient population. Figure B depicts the percentage of the total population in research vs the total SMA patient population.

Ages of Patients Seen by Sites

While five of the sites surveyed only saw children, most saw both children and adults. Minimum and maximum ages seen within these categories are presented below.

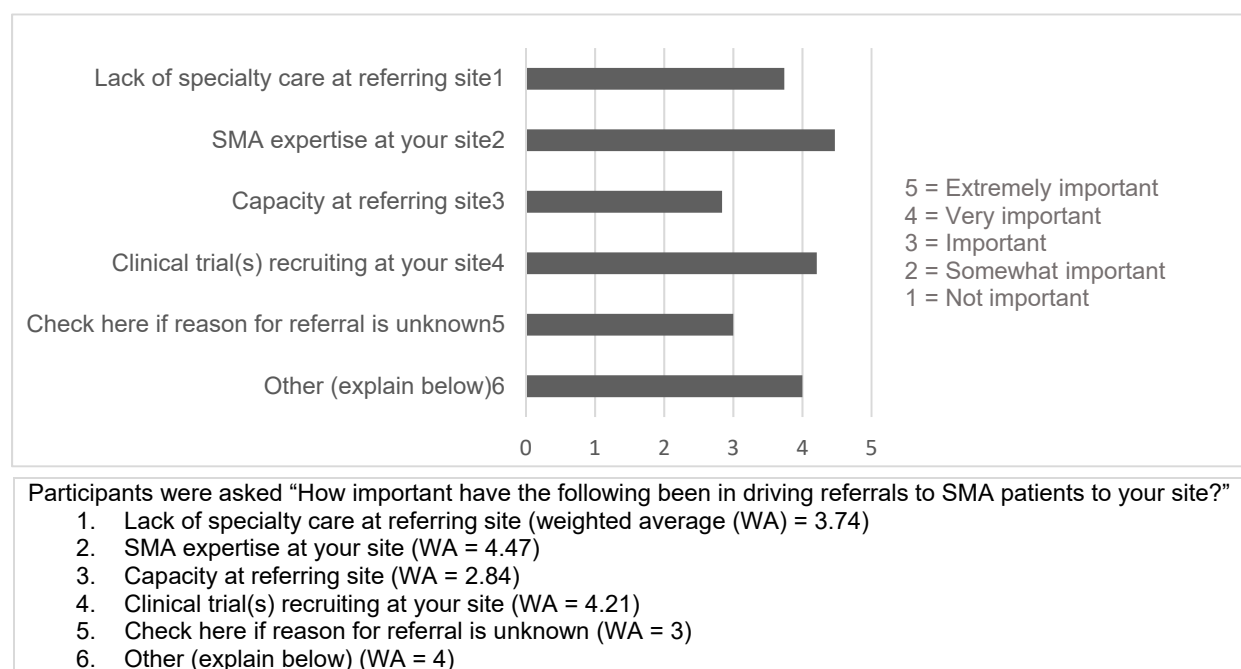
Table 3. Ages of Patients Seen by Neurology Units (in Years)

	n	Youngest Age	Oldest Age
For sites that see children only	5	0	21
For sites that see adults only	0	N/A	N/A
For sites that see children and adults	14	3	100

Sources of Referrals

Respondents were asked how important particular factors were in driving referrals of SMA patients to their clinical trial site. SMA expertise and active clinical trials at the receiving site were the most strongly endorsed factors contributing to referrals, but lack of specialty care and capacity at the referring site were endorsed as important factors as well.

Figure 3. Factors Affecting Patient Referrals (n=19)



II. Studies Underway at Sites Surveyed

In the second major section of the survey, respondents were asked for information about the number of studies underway at their sites. As was expected due to the overall number of studies underway across the country, the total number of studies in SMA varied quite a bit, while there was comparatively less variation within specific types of studies.

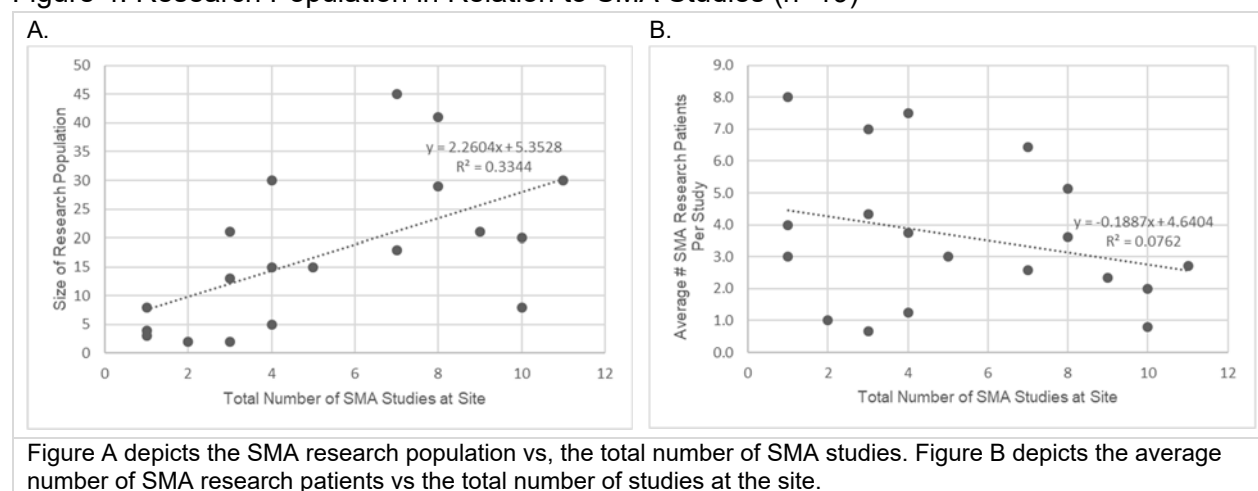
Table 4. Numbers of SMA Studies Underway at Sites (n=19)

	Minimum	Maximum	Mean
Phase I trials	0	2	0.7
Phase II trials	0	6	1.7
Phase III trials	0	4	1.3
Observational/natural history studies	0	3	1.1
Investigator-initiated studies	0	2	0.5
Open-label extension trials	0	3	1.2
Total # studies in SMA (sum)	1	11	5.3
Total # studies within unit (all diseases)*	2	40	14.3

*n=16; sites that reported >40 studies were excluded

To better see the relationship between the total number of studies and the research population, research population sizes were plotted against the total number of studies, as were the average number of SMA research patients per study at sites. In Phase III, this data will be analyzed on a site-specific level to better understand potential capacity across sites, as well as what sites' performance in terms of recruitment. This additional analysis will inform which sites are targeted as part of Phase III activities to increase capacity at sites.

Figure 4. Research Population in Relation to SMA Studies (n=19)



III. Site Staff

Respondents were asked for information about three categories of key staff (principal investigators, clinical trial coordinators, and physical therapists). The detailed results are summarized in the first table below. On average, sites had 4.2 total principal investigators in their unit. The average number of PIs with SMA experience across sites was 2.6. For clinical trial coordinators, sites had on average 6.3 clinical trial coordinators overall; the average number with SMA experience was 3.5. For physical therapists (PTs), sites had on average 5.7 physical therapists overall; the average number with SMA experience was 2.7. Across sites, PIs have on average have more experience with SMA (14.8 years) than either coordinators (3.5 years) or physical therapists (2.3 years).

Table 5. Principal Investigators, Clinical Trial Coordinators, and Physical Therapists: Total Numbers and Experience with SMA

	n	Min	Max	Mean	St Dev
<i>Principal Investigators</i>					
Total # of Principal Investigators*	18	1	10	4.2	2.62
# PIs with SMA experience	19	1	8	2.6	1.71
Average total years of experience	19	0	40	14.8	9.08
Average years experience in SMA	19	2	20	9.0	5.10
<i>Clinical Trial Coordinators</i>					
Total number of coordinators*	18	2	17	6.3	3.51
# coordinators with SMA experience	19	1	7	3.5	1.71
Average total years of experience	19	2	20	10.3	6.44
Average years experience in SMA	19	2	15	3.8	3.37
<i>Physical Therapists</i>					
Total number of PTs	19	0	35	5.7	7.94
# PTs with experience conducting SMA outcome measures in a clinical setting	19	2	5	2.7	1.00
Average years experience conducting SMA outcome measures in clinical trials	19	2	15	5.8	4.24
# PTs with reliability training for conducting SMA outcome measures in SMA clinical trials	19	1	5	2.3	0.82

*Excluded one site which reported 500 PIs and 150 coordinators.

Sites were also asked to report the numbers of other health care professionals they had on staff. Professionals were asked about staff important for providing comprehensive care to SMA patients such as neurologists, nurse practitioners, pulmonologists, GI specialists, occupational

and physical therapists. The second table in this section provides the summary of these results. The average numbers of these health care professionals at sites ranged from two to seven professionals, but there was large variability in staffing across sites. Individual sites had many of the additional support staff, but not necessarily all. No clear trends were identified when comparing the numbers of the key staff to the sizes of research population at SMA sites or the number of SMA studies underway. Sites were also asked to report the fraction of FTE time of these professionals that was dedicated to clinical trials, but an error in the survey prevented sites from providing meaningful information on this question (and a number of sites also reported that they do not calculate FTEs in this way). As a result, that information is not included here.

Table 6. Total Numbers of FTEs within Neurology Units (n=19)

	Minimum	Maximum	Mean	St Dev
Neurologists (n=17)*	2	8	4.1	2.00
Nurse practitioners (n=18)*	0	20	1.9	4.59
Pulmonologists	0	20	3.7	4.77
GI specialist/nutritionist/dieticians	0	23	3.1	5.17
Physical therapists	0	35	5.7	7.94
Occupational therapists	0	31	4.3	7.59
Electrophysiologists	0	7	2.2	1.77
Genetic counselors	0	10	1.9	2.90
Social workers	0	5	1.5	1.26
Principal Investigators	1	30	6.1	7.59
Clinical Research Coordinators	2	20	7.1	5.04
*Excluded two sites which reported >20 neurologists and one site which reported 200 nurse practitioners, as these numbers were dramatically higher than all other sites' numbers.				

To understand the average patient load across sites, the minimum, maximum, and average ratios of research patient to staff across the sites were calculated. These data are summarized below. On average, sites have one PI for every 10 SMA research patients, one clinical research coordinator for every five research patients, and one physical therapists for every seven SMA research patients. Overall, there is one physical therapists for every 30 SMA patients in the total patient population for these sites.

Table 7. Key Health Care Professionals with SMA Experience: Total Numbers and Patient/ HCP Ratios (n=19)

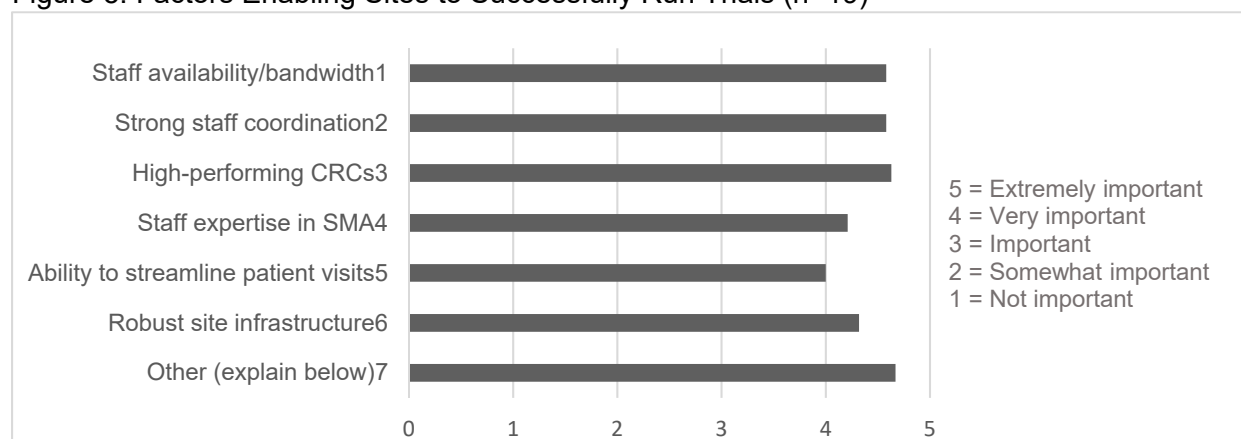
	Minimum	Maximum	Median	Mean	St Dev
<i>Numbers of PIs, Coordinators, and PTs with SMA Experience</i>					
Principal Investigators	1	8	2	2.6	1.7
Clinical Research Coordinators	1	7	3	3.5	1.7
Physical Therapists	2	5	2.0	2.7	1.0
<i>Ratios of Patients to Key Professionals with SMA Experience</i>					
Research Patients/Pis	0.3	30.0	6.7	9.6	9.2
Research Patients/CRCs	0.5	10.0	5.0	5.1	3.0
Research Patients/PTs	1.0	15.0	6.5	6.8	4.9
Total Patients/PTs	6.3	71.7	27.3	30.2	17.9

IV. Site Capacity

Factors that Have Enabled Sites to Successfully Run Trials: Sites were asked to rank the significance of enabling factors including clinical staff bandwidth, staff and site coordination, performance of the clinical trials coordinator, staff expertise in SMA, and site infrastructure. No one factor clearly stood out as most important to successfully

running trials. Staff bandwidth, coordination, and performance of coordinators were all endorsed as extremely important to successful trial management.

Figure 5. Factors Enabling Sites to Successfully Run Trials (n=19)



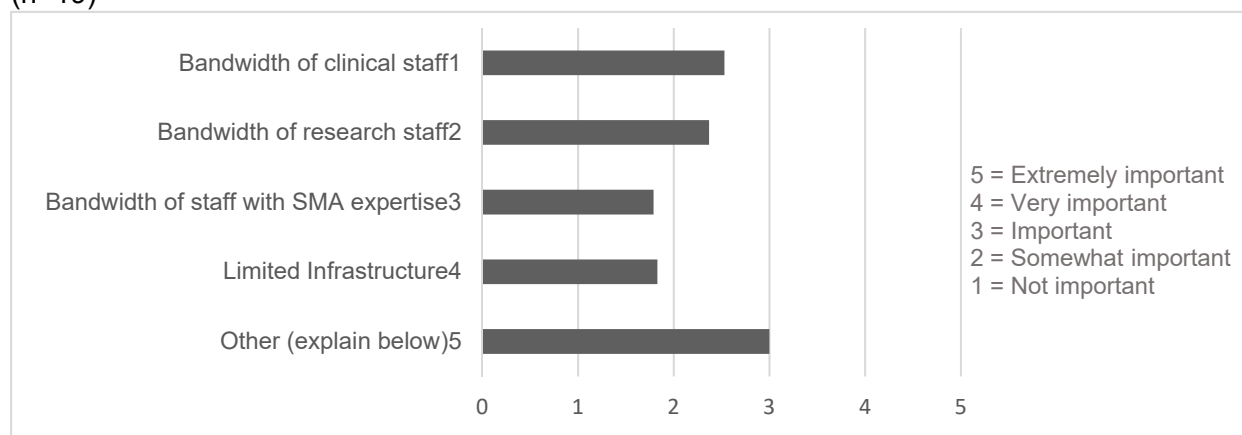
Participants were asked “How important have the following factors been in enabling you to successfully run clinical trials in SMA?”

1. Staff availability/bandwidth in general (WA=4.58)
2. Strong staff coordination in general (WA=4.58)
3. High-performing clinical trials coordinator (WA=4.63)
4. Staff expertise in SMA (WA=4.21)
5. Ability to streamline patient visits (e.g. by coordinating appointments to occur in a single day) (WA=4)
6. Robust site infrastructure (e.g. facilities well-suited to SMA patients/trials) (WA=4.32)
7. Other (explain below) (WA=4.32)

Factors Preventing Sites from Taking on Additional Trials: Sites were asked to rank the significance (on a Likert scale) of two categories of limiting factors related to (a) the site and its staff and (b) patients.

(a) Site and Staff Factors: Potential site and staff limiting factors covered by the survey were clinical staff bandwidth, trial staff bandwidth (including bandwidth of staff with SMA experience specifically), infrastructure, and other factors. Bandwidth of clinical and trial staff emerged as most the most significant factors limiting capacity across sites. However, these were only highly significant for a fraction of sites, and were not significant for about half of the sites. Bandwidth of staff with SMA expertise and limited site infrastructure did not appear to be significant factors. The graph below summarizes the weighted rankings for the individual factors.

Figure 6. Site/Staff-Related Factors Preventing Sites from Taking on Additional SMA Trials (n=19)

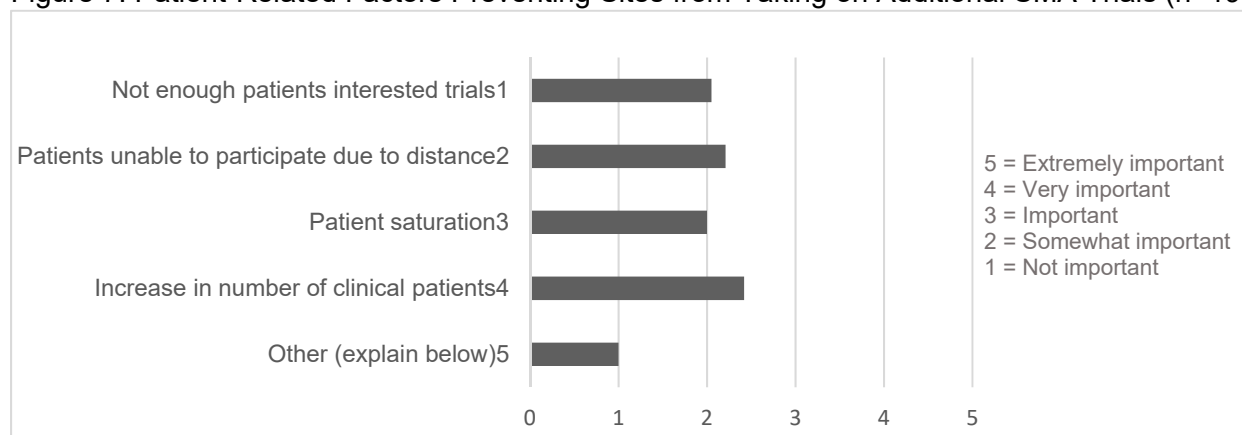


Participants were asked “how significant – if at all – are the following in preventing you from taking on additional SMA trials at this time?”

1. Bandwidth of clinical staff in general (WA=2.53)
2. Bandwidth of clinical trial (research) staff specifically (WA=2.37)
3. Bandwidth of clinical trials staff with SMA expertise (WA=1.79)
4. Limited Infrastructure (e.g. size or number of facilities) (WA=1.83)
5. Other (explain below) (WA=3)

(b) Patient-Related Factors: Limiting factors related to patients that sites were asked about included patient interest, distance from sites, patient saturation due to ongoing open label extension trials, and increased numbers of patients being followed as new treatment options become available. All factors were endorsed as contributing, but there were not any individual factors that emerged as highly significant in limiting capacity. The graph below summarizes the weighted rankings for the individual factors.

Figure 7. Patient-Related Factors Preventing Sites from Taking on Additional SMA Trials (n=19)



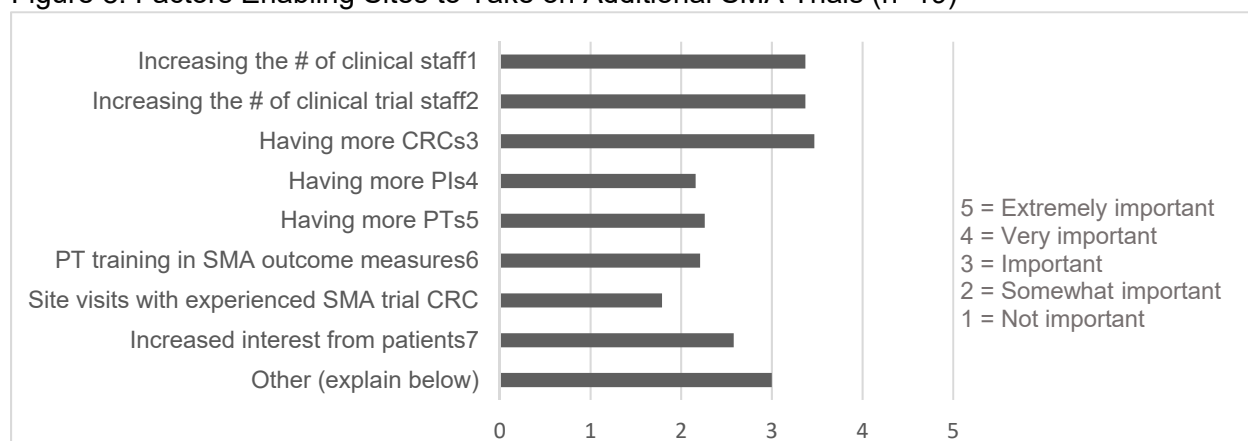
Participants were asked “how significant are the following in preventing you from taking on additional SMA trials at this time?”

1. Not enough patients interested in new trials (WA=2.05)
2. Patients interested in clinical trials but unable to participate due to distance from site (WA=2.21)
3. Patient saturation given existing number of patients being followed as part of open label extension trials (WA=2)
4. Increase in number of clinical patients being followed as new treatment options become available (WA=2.42)
5. Other (explain below) (WA=1)

Opportunities to increase capacity: Sites were asked to rank a series of potential approaches to addressing capacity challenges, and to provide free text suggestions for activities Cure SMA could undertake to support sites. Items ranked by sites included increasing numbers of clinical staff, trial staff, coordinators, principal investigators, and physical therapists; PT training in outcome measures; site visits with an experienced trial coordinator to identify opportunities to improve efficiency; and increased patient interest in trials.

Of these factors, increasing numbers of clinical staff, trial staff, and coordinators would be most helpful to sites. PT training in outcome measures and visits from coordinators would be helpful to a handful of sites. However, about half of the respondents indicated that these activities would not be helpful for their sites. The graph below summarizes the weighted rankings for the individual factors.

Figure 8. Factors Enabling Sites to Take on Additional SMA Trials (n=19)



Participants were asked “how helpful would the following be in increasing your ability to take on additional SMA trials?”

1. Increasing the number of clinical staff in general (WA=3.37)
2. Increasing the number of clinical trial staff, specifically (WA=3.37)
3. Having more clinical research coordinators (WA=3.47)
4. Having more PIs (WA=2.16)
5. Having more PTs (WA=2.26)
6. PT training in SMA outcome measures (WA=2.21)
7. Site visits with experienced SMA trial coordinator to identify opportunities to improve efficiency (WA=1.79)
8. Increased interest from patients in clinical trials (WA=2.58)
9. Other (explain below) (WA=3)

Free-Text Responses: Sites were also given the opportunity to provide free text responses describing other activities Cure SMA might be able to do to help with management of existing patients and to help sites take on new clinical trials. Three themes were identified in the responses:

- Raising awareness of trials amongst the patient community in general was suggested by several respondents.
- Raising awareness about under-utilized sites and assistance with enrollment was also suggested by a handful of sites.
- Grants to support expanded infrastructure and coordinators were also identified as helpful by multiple sites.