

Social Media Methods for Studying Rare Diseases

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KEY WORDS

rare disease, social media, Fontan

ABBREVIATIONS

PB—plastic bronchitis

PHI—personal health information

PLE—protein losing enteropathy

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www.pediatrics.org/cgi/doi/10.1542/peds.2013-2966

doi:10.1542/peds.2013-2966

Accepted for publication Feb 10, 2014

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abstract



For pediatric rare diseases, the number of patients available to support traditional research methods is often inadequate. However, patients who have similar diseases cluster “virtually” online via social media. This study aimed to (1) determine whether patients who have the rare diseases Fontan-associated protein losing enteropathy (PLE) and plastic bronchitis (PB) would participate in online research, and (2) explore response patterns to examine social media's role in participation compared with other referral modalities. A novel, internet-based survey querying details of potential pathogenesis, course, and treatment of PLE and PB was created. The study was available online via web and Facebook portals for 1 year. Apart from 2 study-initiated posts on patient-run Facebook pages at the study initiation, all recruitment was driven by study respondents only. Response patterns and referral sources were tracked. A total of 671 respondents with a Fontan palliation completed a valid survey, including 76 who had PLE and 46 who had PB. Responses over time demonstrated periodic, marked increases as new online populations of Fontan patients were reached. Of the responses, 574 (86%) were from the United States and 97 (14%) were international. The leading referral sources were Facebook, internet forums, and traditional websites. Overall, social media outlets referred 84% of all responses, making it the dominant modality for recruiting the largest reported contemporary cohort of Fontan patients and patients who have PLE and PB. The methodology and response patterns from this study can be used to design research applications for other rare diseases. *Pediatrics* 2014;133:e1345–e1353

The National Institutes of Health defines a rare disease as a disease with an overall prevalence of <200 000 affected individuals in the United States.¹ For patients afflicted with rare diseases, medical care is complicated by insufficient knowledge regarding the disease's pathogenesis, progression, and treatment. As the number of patients available for research at a single center is typically inadequate, multicenter research efforts are often required to gain advanced insight. However, multicenter studies are more expensive and time consuming, and can be difficult to coordinate. For these reasons, relatively few multicenter studies of rare diseases are undertaken, and the majority of rare diseases continue to be poorly understood.

In pediatric cardiology, single ventricle heart diseases have an incidence of 4 to 8 out of 10 000 live births.² Staged surgical palliation to the Fontan procedure is the standard approach to treat children born with these diseases. Following this operation, patients may develop specific complications, including protein losing enteropathy (PLE) and plastic bronchitis (PB). PLE is estimated to occur in 1% to 11% of Fontan patients, whereas PB is estimated to occur in 1% to 5%.^{3–6} Although the true prevalence of PLE and PB is unknown, based on single ventricle heart disease incidence and post-Fontan survival rates, PLE and PB are likely exceedingly rare diseases with a prevalence of <2000 patients in the United States. As such, both PLE and PB are poorly understood; disease knowledge stems largely from case reports. Multicenter research efforts for PLE and PB are lacking.

New approaches to research can avoid the limitations typically imposed by disease rarity. Despite the paucity of patients who have PLE or PB at any 1 particular cardiac center, patients

group together “virtually” online in larger numbers. Social media outlets such as Facebook pages, Twitter follows, message boards, and e-mail lists exist for PLE and PB, and these sites are frequented by patients and parents seeking information and support. We hypothesized that if participation in research were offered online, patients would participate in larger numbers than would be obtainable through cardiac center-based projects. Furthermore, we hypothesized that participants would recruit each other, similar to the information-sharing that drives all social media. To determine whether such a social media-based research recruitment process would be feasible, we created and posted an online survey designed to gather patient-reported data from both non-complicated, “healthy” Fontan patients and patients who have PLE or PB.

METHODS AND RECRUITMENT STRATEGIES

Survey Instrument Creation

After a thorough review of the PLE and PB literature, we created a survey tool consisting of questions regarding patient demographics, medical and surgical history, symptoms, associated illnesses, home environment, treatment history, and current medical therapy. The tool was specifically designed with the intent of having both “healthy” and complicated Fontan patients participate. Cardiologists from our institution (Drs Schumacher, Fifer, Russell, and 2 additional non-author cardiologists) vetted the survey to assure the completeness and relevance of the information queried. An internet survey expert (Dr Zikmund-Fisher) reviewed the survey to assure optimal structure and validity of question forms. We included several questions regarding the participant's location and how he/she was referred to the

survey. Whenever possible, questions maintained a yes/no, short multiple-choice, or check-box format. All questions were written at a middle school reading level or lower, and any medical terms used were plainly defined.

We administered the survey using Qualtrics survey software (Provo, UT), which includes dynamic routing capabilities. Based on responses to screening questions, the survey structure adjusted to only administer questions pertinent for all Fontan patients, those patients who had PLE, and those who had PB. For example, only individuals who answered “yes” to the question “have you ever been diagnosed with PLE” would gain access to further PLE questions. We piloted the survey in talk-aloud sessions with healthy Fontan patients, patients who had PLE, and patients who had PB from our own center and refined the instrument based on feedback. We allowed most questions to be skipped so that people who wanted to continue the survey could do so without answering questions they did not know or understand. The survey consists of 31 questions/items for uncomplicated Fontan patients, 52 items for patients who have PLE, 55 items for patients who have PB, and 76 items for patients who have both. Time to complete the survey averaged 9 minutes for uncomplicated Fontan patients and 22 minutes for complicated Fontan patients. A copy of the survey is available for viewing at this website: <http://tinyurl.com/UmichFontanSurvey>

Social Media and Security

The survey was linked to 2 online portals from which patients could gain access: a study-specific Facebook page (<https://www.facebook.com/#!/UMFontan>) and a web-based portal from the University of Michigan Congenital Heart Center's home page ([e1346 SCHUMACHER et al](http://www.</p></div><div data-bbox=)

med.umich.edu/mott/congenital/research/FontanFacepage.html). A link to the survey was available at each site. Security and the potential to reveal patient-identifying information in a social media forum was a significant concern. Qualtrics software has SAS 70 Certification meeting the privacy standards imposed on health care records by the Health Insurance Portability and Accountability Act (HIPAA). All Qualtrics accounts are hidden behind passwords, and all data are protected with real-time data replication. To protect patient confidentiality, we elected to make the survey itself anonymous and unlinked to individual patients via direct identifying information. The Facebook page was maintained by the study team, but any patients could freely post information to the page. The study team left all message postings in place on the Facebook page. The study was approved by our center's Institutional Review Board, and an informed consent message preceded the survey. Children under the age of 18 years completing the survey granted assent in addition to the consent given by their parents.

Participant Compensation, Recruitment, and Accessing Online Communities

We offered a direct report of the results to any participants who requested them. A study-specific e-mail address was created and posted at the end of the survey with instructions to e-mail the study team with questions or to request results after the study's completion.

We required research participants to be age 15 years or older to participate. Parents were allowed to answer for younger children.

Because 1 of the study's stated aims was to evaluate whether patient recruitment would be organically expansive and self-sustaining, active recruitment by the study team was

limited but did target the different online access points of the survey. To access the Facebook community, the study team posted a short notification ("wall post") about the survey on 2 existing, patient-run, PB Facebook pages. Other than on our own pages, no further Facebook posts were made by the study team for the duration of the study. However, on our own page, we made a series of posts detailing the study's progress and encouraging page visitors to share our study's information.

To access non-Facebook social media sites, we used queries to our study's e-mail account. When an individual requested results from the survey, we replied with an e-mail thanking them for participation and encouraging them to refer any other individuals who may be interested in the study. If the individual replied with a specific organization that he/she thought should be notified, we would send an e-mail to that organization stating that a study-participant had referred us to them and provide a brief study description. If the organization chose to post or publicize the study, we assisted them as necessary.

To access non-social media-based internet users, a series of short Google ads were placed in response to the search terms "protein losing enteropathy" and "plastic bronchitis." The advertisements appeared alongside Google searches with these keywords and were maintained throughout the study.

Response Validation

Given that responses were not linked to patient identifiers, traditional methods of comparing patient reports to medical records were impossible. Instead, a series of planned quality control measures were used. First, surveys that did not include birth years and years of operations were excluded. Second, survey responses were evaluated to

assure that they appeared medically rational in terms of surgical dates and progression, and dates of complication diagnoses. Responses in which birth-date, surgical dates, and Fontan complication onset did not follow a feasible chronologic pattern were excluded.

As an additional analysis to support external validity of the survey for the total Fontan population, we compared our participants' demographic and historical information to patients reported in a recent Pediatric Heart Network Fontan cross-sectional study.⁷

Statistical Analysis

Standard descriptive statistics outlined participant characteristics overall and stratified by "healthy," "PLE," "PB," and "both PLE and PB." Group comparisons between Fontan patients with and without complication were made using χ^2 tests or Fisher's exact tests, as appropriate, for categorical variables and Wilcoxon rank sum tests for continuous variables. Odds ratios and 95% confidence intervals for being diagnosed with PLE or PB were also reported. For the validation with the existing Fontan cross-sectional study, we used appropriate 2-group comparisons including χ^2 tests and *t* tests. All analyses were performed by using SAS version 9.3 (SAS Institute, Cary, NC).

RESULTS AND RESPONSE OBSERVATIONS

Responses

After 1 year of open study enrollment, a total of 855 individuals who had a Fontan palliation completed at least 1 survey question. Of these, a total of 671 respondents (95% parents and 5% patients) completed the survey with valid responses, making the overall survey completion rate 78%, including 76 patients who had PLE and 46 patients who had PB. Of these, 7 individuals reported having both PLE and PB.

The number of completed responses over time is displayed in Fig 1. Approximately 2 weeks after the survey's online launch, the response rate markedly increased, with more than 500 individuals completing the survey over the next 1.5 months. During this time, several participants shared the survey within their online social communities, including other Facebook pages, tweets, online congenital heart disease patient forums, and e-mail listservs. Study-specific communications by patient-run organizations to their constituents that are known to the investigators are noted in Fig 1. For the next 8 months, responses slowed but continued at a steady rate of approximately 10 per month. At 11

months, the responses again markedly increased following a blog post by a study author on a heart-specific social network (noted on Fig 1). Presumably this posting accessed a group of online Fontan patients who had not previously been aware of the study.

Limited sociodemographic information was collected. Of respondents, 63% were male. The median patient age was 5 years (interquartile range, 5–12 years). Self-reported race was as follows: 83.5% white/Caucasian, 1% black/African American, 2.5% Hispanic, 0.7% Asian, 0.3% Native American, 0.3% Arabic, 0.1% Pacific Islander, 1% other, 9.1% multiple races, 1.3% unknown. A total of 574 responses (86%) came from within the United States, (48 out of 50

states). The response distribution largely paralleled the US population (Fig 2). Additional respondents originated from 19 additional countries on 6 continents, including Australia (29), Canada (22), the United Kingdom (11), the Netherlands (8), Germany (7), New Zealand (5), Ireland (2), and 1 response each from Belgium, Brazil, Croatia, Finland, France, Lithuania, South Africa, Spain, Switzerland, the United Arab Emirates, Venezuela, and Zimbabwe.

The respondents reported their referral source for the survey (Fig 3). Facebook was cited as the leading referral source with 394 respondents (59%). Internet forums (174 respondents) and other websites (75 respondents) made up the bulk of the remaining

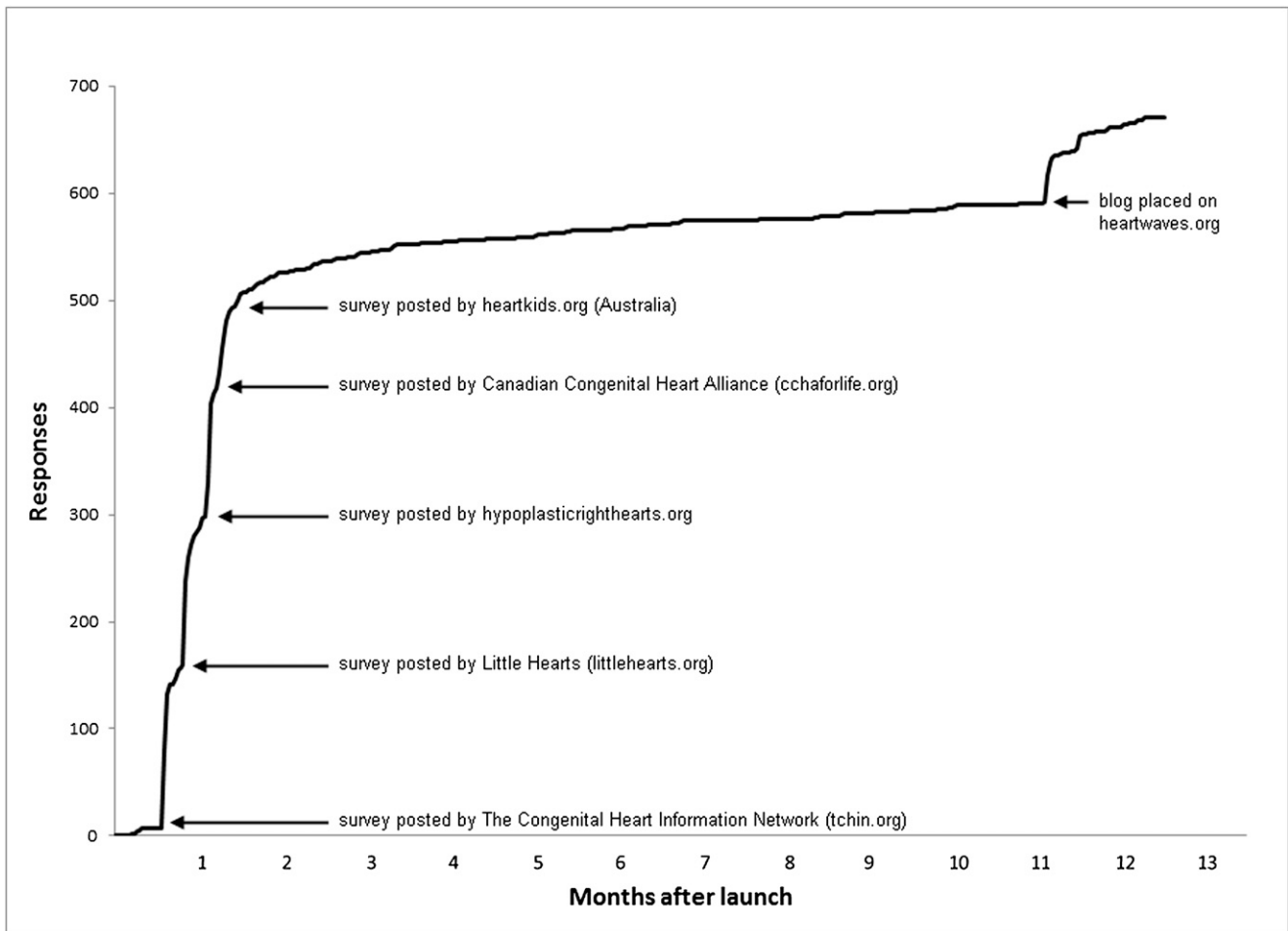


FIGURE 1
Survey responses over time.

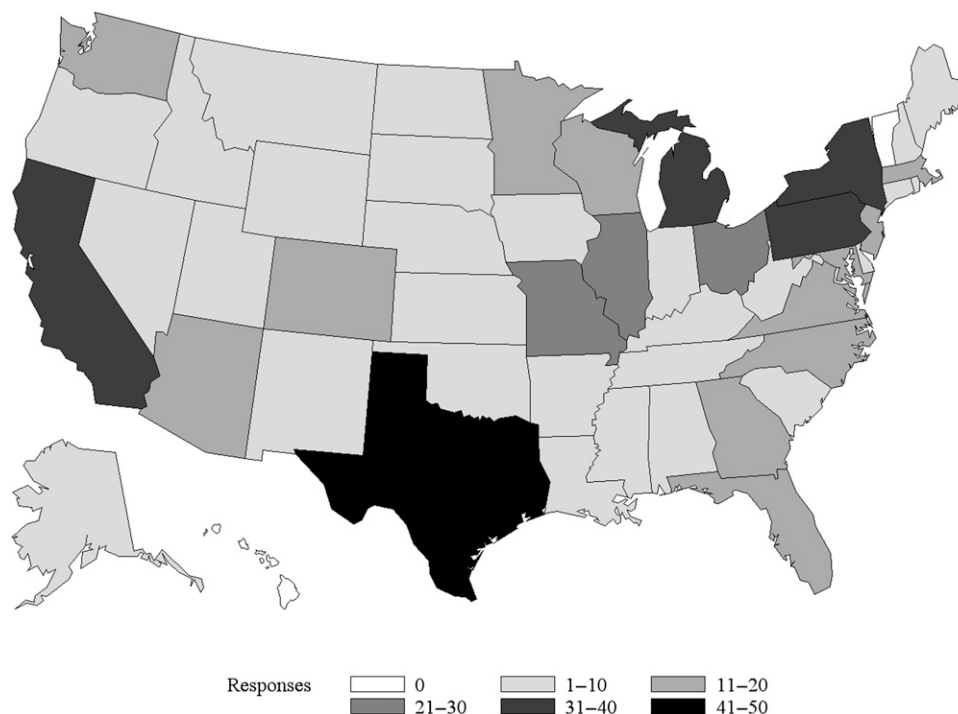


FIGURE 2
Responses by state.

referrals. In total, social media was the dominant referral modality, contributing 84% of referrals compared with 11% from non-social media internet sources, 3% non-internet, and 2% from an unknown source.

Comparisons Between PLE/PB and Healthy Fontan Patients

Table 1 shows limited demographic and cardiac surgical history data. Although complete disease-specific

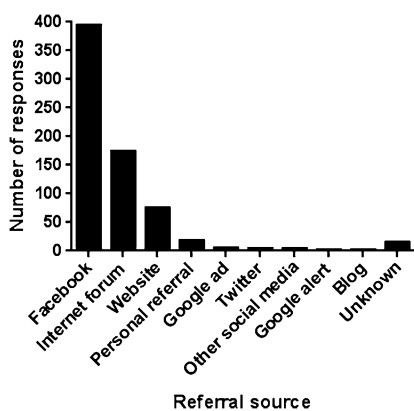


FIGURE 3
Sources of participant referral.

details are beyond the scope of this report, some of the information from the analysis allowed interesting insight into the characteristics of respondents. We specifically wondered whether a response bias could occur in which patients who had more complex medical/surgical histories were more likely to participate. In Table 1 under “other surgeries,” the items “diaphragm plication” and “additional intra-cardiac or great vessel surgery” represent patients who had additional, unplanned surgeries apart from the typical, staged surgical palliation, implying a more complicated course. Fontan patients who had PLE and PB were more likely to have unplanned surgeries, which gives insight into pathophysiology. In contrast, Fontan patients who did not have PLE or PB reported low rates of unplanned surgery, indicating likely less complex courses. This suggests that both uncomplicated and complicated patients responded to the survey, and the complex history response bias is not apparent.

Response Validity

To assure internal validity, of the 855 individuals who logged into the study and answered at least 1 question, 75 were disqualified for not reporting a Fontan surgery. An additional 99 respondents were disqualified after failing to report Fontan surgical dates or birth dates. Finally, 10 respondents were disqualified for reporting birth and/or specific surgical dates that were deemed medically unfeasible. External validity was demonstrated when the final survey cohort was compared with the recent Pediatric Heart Network cohort⁷ and no differences in participant gender, age, and type of single ventricle heart disease were found.

Social Media Metrics

Facebook maintains its own set of metrics that can be used to measure a page’s online impact. The study’s Facebook page received 190 “likes.” Additionally, Facebook tracks metrics regarding the impact of each message

TABLE 1 Patient Characteristic Comparisons in Fontan Patients With and Without Complications

	Overall (n = 671)	PLE or PB				P value
		None (n = 556)	PLE (n = 76)	PB (n = 46)	Both (n = 7)	
Respondent						0.058
Parent, (%)	637 (95)	529 (95)	69 (91)	46 (100)	7 (100)	
Patient, (%)	34 (5)	27 (5)	7 (9)	0	0	
Male gender, (%)	421 (63)	353 (63)	45 (59)	27 (59)	4 (57)	0.40
Age at survey (y), median (IQR)	7 (5–12)	7 (5–11)	11 (7–17.5)	7.5 (6–12)	11 (7–13)	<0.0001
Age at Fontan (y), mean ± SD	3.3 ± 2.2	3.4 ± 2.2	3.1 ± 1.8	2.9 ± 1.4	2.7 ± 1.3	0.15
Time since Fontan (y), median (IQR)	4 (2–9)	4 (1–8)	8 (4–13)	4.5 (3–9)	8 (4–10)	<0.0001
Other surgeries ^{a,b}						<0.0001
Norwood, (%)	319 (48)	252 (45)	45 (59)	26 (57)	4 (57)	
BT shunt, (%)	291 (43)	248 (45)	23 (30)	21 (46)	1 (14)	
Glenn, (%)	515 (77)	437 (79)	50 (66)	33 (72)	5 (71)	
Hemifontan, (%)	114 (17)	84 (15)	20 (26)	12 (26)	2 (29)	
PA banding, (%)	81 (12)	67 (12)	11 (14)	3 (7)	0	
Diaphragm plication, (%)	30 (4)	17 (3)	9 (12)	6 (13)	2 (29)	
Other major intracardiac/great vessel procedure, (%)	43 (6)	26 (5)	13 (17)	6 (13)	2 (29)	
Heart disease etiology						0.002
Hypoplastic left ventricle, (%)	311 (46)	244 (44)	47 (62)	25 (54)	5 (71)	
Hypoplastic right ventricle, (%)	244 (36)	219 (39)	15 (20)	11 (24)	1 (14)	
Nonspecific single ventricle, (%)	116 (17)	93 (17)	14 (18)	10 (22)	1 (14)	

All values represent *N* (%) unless otherwise specified; column percentages reported. *P* values from 2-group comparison between “none” (no complication) and “PLE, PB, or both” (any complication).

^a Categories are not mutually exclusive.

placed on the site. At the time of drafting this manuscript, an author posted a message on the Facebook page regarding study progress. The message had a “reach” of 1357, meaning 1357 unique individuals saw the message on Facebook. Additionally, 51 “reposted” our message on their own Facebook pages, further raising study visibility.

Cost

No monetary costs were incurred by the study team. However, we acknowledge an institutional account provided access to Qualtrics survey software, which costs approximately \$2500 to \$3000 for individual access. An institutional grant funded the Google ads. Google ads use a pay-per-click structure, and the price of each “click” is set based on the popularity of the search term. Google contacts estimated the terms “Fontan,” “protein losing enteropathy,” and “plastic bronchitis” would cost anywhere from \$0.05 to \$1.00 per click. Only 5 respondents were referred from a Google ad, meaning the cost of Google ads for this study was very small.

LESSONS LEARNED AND FUTURE POSSIBILITIES

This study resulted in the largest report of contemporary, uncomplicated Fontan patients and patients with Fontan-associated-PLE and PB. Patients directly reported a rich set of data regarding their own disease history, risk factors, course, and therapy, which is not available elsewhere in the medical literature for either PLE or PB. By accessing established, social media-based patient communities, over a relatively short time period (1 year) this study successfully recruited a previously unattained number of patients with low associated costs. The majority of participants came from social media communities. Before social media’s dominance in our society, these results would not have been achievable. This study’s methodology may serve as a valuable approach for acquiring meaningful data for other rare diseases.

Social media is a form of communication based on highly interactive, electronic platforms in which individuals

and communities share, co-create, modify, and discuss user-generated content.⁸ Facebook, the largest social media platform, recently reported 1.11 billion users with 655 million daily active users.⁹ Given this enormous number of potential study subjects, medicine has a growing interest in the use of social media in the context of research. One study showed that families dealing with rare diseases are active in social media communities,¹⁰ and a few reports demonstrate the use of social media to recruit subjects for broad population-based studies, studies of more common diseases, or small studies of less common diseases.^{11–14} To our knowledge, only 1 study has reported using primarily social media in a prospective study of a very rare disease: an online support group of 12 individuals was accessed to obtain consent for a study of spontaneous coronary artery dissection.¹⁵ By contrast, our study demonstrates the feasibility of using social media to reach a significantly larger number of participants via multiple online communities using only online resources. In

addition, the study was specifically designed with a control group for comparison, and all information was entirely patient provided.

The observed response patterns illustrate social media's advantages. It allows individuals to both participate in the study and recruit other participants, which makes each participant a pseudo-coinvestigator.¹⁶ After gaining access to the online group of Fontan patients, the marked increase in responses was consistent with the information-sharing inherent to social media. Often a participant shared the study with other members of their online community, who in turn shared with their own contacts. Given no space or time constraints online, this sharing and subsequent participation occurred very quickly. In internet terms, the study recruitment "went viral" in the Fontan community. Also consistent with social media, geography did not affect participation. Responses were evenly distributed across the United States. Responses from around the world were equally fascinating and introduced the potential of studying rare diseases on a global basis. The need for multilingual study tools is apparent, however, to enable patient access to participation on a global basis. Although accurate, accessible translation software is increasingly available, the complexities of research-specific questions continue to necessitate human expertise and international collaborators to insure accuracy.

Despite the advantages of social media to power studies, it must be noted that some patient groups may be less likely to participate if a study is only offered via social media. In our study, the percentage of patients identifying themselves as African American or black, Hispanic, or Asian appeared lower than other reports of large groups of Fontan patients.⁷ Possible explanations for this discrepancy include the response

option of mixed-race heritage being offered in our study or related to responses from countries with different racial compositions. However, racial differences in social media use may be present. In the United States, racial differences in accessing personal health records have been reported, and African Americans use electronically accessible health resources significantly less than whites.¹⁷ The reasons behind racial disparities in using electronic health resources remains unclear, but it is reasonable to assume that our results may be explained by similar use patterns for electronic health research. To be inclusive of all race groups, future studies should specifically address these concerns with efforts to access patient groups in other ways, either electronically or otherwise.

A primary aim of this study was to determine whether a social media-based approach to recruiting would be organically expansive and self-sustaining, thus active, multichannel recruitment was intentionally not done. We now believe future studies could be enhanced by additional multichannel recruiting. Patient-run, disease-specific communities were a major asset in recruiting. Partnering with these organizations at the outset of a study could facilitate improved access to participants. Our study was conceived at the beginning of Twitter's rise to prominence. We did not use Twitter for recruitment, and Twitter accounted for just 4 responses. However, Twitter's marked rise in popularity makes it an attractive possibility for use in future studies. Tweet chats, live Twitter events focused around a topic, are rising in popularity and could be used to improve engagement of the study population. Live sessions moderated by the study team and dedicated to discussion of particular aspects of a disease would likely raise awareness of the study team and its efforts within the

community. Similarly, given that our population appeared interested in continued learning about their disease, creation of study-run, sustained, online patient forums should be considered. In addition to giving patients a community of people who have shared experiences, these forums would continue to engage the population over time, making them available for future studies, and allow patients themselves to identify future research directions. Next, engaging other providers directly would allow them to bring the study to their own patients' attention and further enhance participation. Finally, offering non-electronically-based participation may allow improved participation for patients uncomfortable with online participation or transmission of personal health information (PHI).

Although social media powered this study and offers distinct advantages for rare disease research, steering clinical research to this new avenue is not without some concerns. Ethicists have begun to point out the potential concerning implications of broad social media-based information sharing. The necessity of research-board regulations for patient-directed research and the role-blurring of investigator and participant when the participants are the main study-recruiters are issues that have not been adequately addressed by the medical community.¹⁶ As this research strategy becomes more prevalent, such issues will require broader discussion. Security of electronic PHI (ePHI) also requires consideration. In January 2013, the US Department of Health and Human Services published the Omnibus Final Rule, which modified HIPAA security standards to include any entity that "creates, receives, maintains, or transmits PHI."^{18,19} In short, any entity, including an internet service provider, that deals with online ePHI is now held to the same HIPAA standards as medical providers. From a research

perspective, all information queried and cataloged in an electronically-based study must meet this standard. In our case, the software and data storage used for the study (Qualtrics) meets the privacy standards imposed on health care records by HIPAA. Additionally, the Final Rule was not necessarily applicable to us owing to the anonymity of the study. Anonymous information is not considered PHI. We do, however, acknowledge that our survey collected indirectly identifying information; information such as surgical dates and type of heart disease could be used to identify an individual. The proper approach to protecting indirectly identifying information in any format, not just electronic, is debated by ethicists and review boards.²⁰ We limited the specificity of data to make it unable to be traced back to a unique individual, for instance by asking for the year of operation rather than a specific date. However, given that the line between anonymous and identifying information is not always distinct, we would recommend that any study of human subjects use technology that formally meets HIPAA standards. Social media modalities may be excellent

tools to recruit patients, but they should not be used to transmit or store study data.

Our study has limitations. First, it is unclear whether the participants in the online study are representative of the total population of Fontan patients. For gender, age, and heart disease etiology, our cohort was not different from the Pediatric Heart Network Fontan cohort. However, the lack of observed differences does not completely assure that our cohort was truly representative, particularly given the potential for race-based disparities. Second, because the study was anonymous, there was no way to validate the participants' responses using traditional methods in clinical research, typically via comparison with the medical record. Third, there is no way to assure that individuals who claimed to be Fontan patients actually were Fontan patients or had the complications that they reported. We readily acknowledge these limitations and that similar limitations could occur in all research performed using this methodology. However, with no incentive other than information, individuals should have no motivation to knowingly provide false information. The study

was specifically designed so that the information queried could be provided by patients, and survey piloting demonstrated this to be true. The study's validity checks assured that reported information made medical sense. All of these points indicate the study's results are more likely to be accurate. The data in this type of study do not prove anything, but it can be highly instructive. For a rare disease with significant knowledge limitations, suggestive information may be extremely valuable in directing and spurring new research.

CONCLUSIONS

We have detailed the methodology, patient response characteristics, and lessons learned from a social media-powered study of the rare diseases Fontan-associated PLE and PB. This study resulted in the largest reported contemporary cohort of Fontan patients and patients who have PLE and PB. The study took only 1 year to complete and was performed with minimal expense. Social media is a promising tool for powering rare disease research. This methodology may serve as a guide to design needed research for other rare diseases.

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: This study was supported in part by a Griese-Hutchinson-Woodson Foundation grant (KRS), Congenital Heart Center, University of Michigan, and an institutional Google grant, University of Michigan. Dr Stringer is supported by a grant from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD; HD065594). Funded by the National Institutes of Health (NIH).

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.