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Research priorities in single ventricle heart conditions: a UK national study

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Abstract

Objective—To bring together stakeholders in the United Kingdom to establish national priorities for research in single ventricle heart conditions.

Methods—This study comprised two surveys and a workshop. The initial public online survey asked respondents for up to 3 questions they would like answered by research. Responses were classified as: unanswered, already answered, or unable to be answered by scientific research. In the follow-up survey, unanswered questions were divided into categories and respondents were asked to rank categories and questions by priority. A stakeholder workshop attended by patients, parents, healthcare professionals, researchers and charities was held to determine a final list of research priorities.

Results—128 respondents posed 344 research questions, of which 271 were classified as unanswered, and after removing duplicates, 204 questions remained, divided into 20 categories. 56 (49.1%) respondents successfully ranked categories and questions in the second survey. 39

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Ethical standards: The authors assert that this work complies with the ethical standards of the relevant national guidelines and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the Ethical Review Committee at the University of Birmingham, UK.

Contributors: NED, SH and PFC devised the study. NED, VMS and PFC obtained funding. NED coded the electronic surveys. NED, VMS, CJB and AJP reviewed the questions and revised the wording, with PFC as the additional reviewer, as required. NED chaired the workshop which was attended by all authors and collaborators. NED wrote the first draft of the manuscript which was critically revised by all authors.

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participants attended the workshop, drawing up a list of 30 research priorities across 9 priority categories: Associated co-morbidities, Brain & neurodevelopment, Exercise, Fontan failure, Heart function, Living with a single ventricle heart condition, Management of the well-functioning Fontan circulation, Surgery & perioperative care, and Transplantation, mechanical support & novel therapies.

Conclusions—Through a multi-stage process, we engaged a wide range of interested parties to establish a list of research priorities in single ventricle heart conditions. This provides a platform for clinicians, researchers and funders in the UK and elsewhere to address the most important questions and improve outcomes in these rare but high-impact congenital heart defects.

Keywords

single ventricle heart conditions; Fontan circulation; research priorities; patient involvement

Introduction

Single ventricle heart conditions are a collection of congenital cardiac defects in which one of the ventricles is insufficiently developed or compromised such that it is unable to support an adequate cardiac output. With an incidence of 2-3 in 10,000 live births,[1,2] it includes diagnoses such as hypoplastic left heart syndrome, tricuspid atresia and unbalanced atrioventricular septal defect. Whilst initial surgical palliation varies by type, their paths commonly converge around 3-4 years of age to undergo the Fontan procedure,[3] whereby the functioning ventricle is used to support the systemic circulation with passive blood flow in series to the lungs. The success of surgical programmes over the last 30 years has led to an increasing number of children and adults living with a Fontan circulation, currently estimated at over 3,000 in the United Kingdom,[1] and up to 70,000 worldwide,[4] with the population predicted to double over the next 20 years in developed countries.[1,5] However, this inherently inefficient circulation predisposes to multiple late complications,[6,7] with half affected by a major complication before reaching adulthood.[8] A 40-year old patient with Fontan physiology has an 18% 5-year risk of death, comparable to that of a 75-year old in the general UK population.[9]

Patients with single ventricle heart conditions have complex healthcare needs, requiring multiple operations often from birth and lifelong, multi-disciplinary follow-up in specialist centres.[10] Ongoing physiological and psychosocial issues place a considerable burden on patients and their families with a significant reduction in quality of life.[11] Whilst there are expectations of improving outcomes,[12] the Fontan circulation remains a life-limiting condition with limited treatment options; it is the highest risk diagnosis for heart transplantation yet is the least amenable to mechanical circulatory support.[13] Consequently, there is a demand for research to understand the impact of living with this condition and improve outcomes for patients and families throughout their journey. The International Fontan Interest Group has been established as a collaborative initiative to improve outcomes and has called for engagement of stakeholders to direct research priorities.[4] We therefore brought together interested parties in the UK to establish priorities for research in single ventricle heart conditions.

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Materials & Methods

The study was developed in collaboration with *Little Hearts Matter*, the UK national charity for single ventricle heart conditions.[14] As it blurred the boundaries between scientific research and public engagement,[15] approval was obtained from the Ethical Review Committee, University of Birmingham (ERN_17-0902). Our methodology was informed by the James Lind Alliance [16] and Cochrane Tobacco Addiction Group [15] as we explicitly aimed to reach a wide range of stakeholders including patients, their relatives, healthcare professionals, researchers, charities, funders and policy makers. The study comprised three stages: an initial public survey; a follow-up ranking survey of respondents; and a workshop of invited parties.

Stage 1 survey – identifying gaps in knowledge

An initial cross-sectional, self-administered, public survey was conducted using REDCap, a secure online platform.[17] An electronic link was disseminated by two national patient charities, *Little Hearts Matter* and *The Somerville Foundation*, via email, newsletters and social media (Facebook, twitter). Professional groups were contacted via the organisational mailing lists of the British Congenital Cardiac Association (BCCA), Society for Cardiothoracic Surgery (SCTS) and Paediatric Intensive Care Society Study Group (PICS-SG), and publicised at national meetings. UK-based researchers, heart charities, research funders and NHS commissioners of congenital heart services were contacted directly via email.

Respondents were asked: ‘What questions would you like to see answered by future research for patients who have a single ventricle heart condition?’ and invited to pose up to 3 questions. Additional demographic data was collected on their: role; age (patients); relationship with a patient (relatives); and institution (professionals). Consent was obtained for the storage, analysis and anonymous reporting of data, and a study email address was provided to enable withdrawal of consent and/or data, if required. Respondents were asked to provide their name and email address to allow re-contact for stage 2.

The survey remained open for 12 weeks after which all responses were collated and reviewed according to a predetermined process.[15] Submitted questions were screened by at least two reviewers (NED, VMS, CJB, AJP) to remove duplicates and any that fell outside the scope of the study. The remaining questions were rephrased for clarity and consistency of terminology, as required, and classified according to the current literature as: *unanswered* by current research; *already answered* by published research; or *unable to be answered* by scientific research. Any disagreements were resolved by consensus, involving an additional reviewer (PFC) when necessary. Questions considered *unable to be answered* by research were discarded whilst those most commonly deemed to be *already answered* were collated and lay summaries of the explanation with supporting evidence published in the *Little Hearts Matter* newsletter. Valid *unanswered* research questions were allocated into one or more topic categories according to emerging themes and progressed to the next stage.

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Stage 2 survey – prioritising gaps in knowledge

Respondents who provided an email address were sent a personalised link to a second REDCap survey, enabling tracking of responses and targeted reminders. Participants were asked to rank the emerging research categories from stage 1 in order of priority for future research, from 1 ‘most important’ to 20 ‘least important’. For their top 3 categories, they were asked to similarly rank each question within each category [15].

The second survey remained open for 4 weeks with a reminder sent after 2 weeks. Fisher’s exact test was used to compare response rates. Any responses with insufficient data were excluded. Completed responses were collated and categories assigned a score inversely proportional to their ranking, such that the highest-ranked scored 20 points down to 1 point for the lowest-ranked; a category received an additional 10 points each time it was ranked in a respondent’s top three. By combining these scores, the highest-ranking categories were taken forward to the next stage, along with the five to seven highest ranking questions in each.

Stage 3 workshop – establishing research priorities

Participants were invited to take part in the workshop to represent all those affected by, caring for, or conducting research into single ventricle heart conditions. An iterative process of invitation was used to ensure an adequate balance by role, age/experience, gender and location, with the first invitations sent out eight weeks in advance. Patients and parents who had responded to the surveys were contacted via email, with further participants recruited via social media. A broad range of healthcare professionals were invited from every tertiary congenital heart disease programme in England.

Workshop participants were provided with a booklet in advance, containing information about the study and the list of categories and questions prioritised at stage 2. Written consent was obtained for participation, digital recording of discussions, data sharing and being named as a collaborator. The workshop comprised small and large group discussions (chaired and facilitated by NED), with participants seated at round tables of six or seven according to a predetermined plan to achieve mixed groups by role, experience and location; this ensured that patients/parents were not on the same table as their direct healthcare providers. All participants were encouraged to share their views, respect the views of others, and ensure that they all had the opportunity to express their opinions. Specialist nurses and charity representatives were available throughout the day so that participants could talk through any difficult issues in a private breakout room.

In the morning, the small groups were asked to identify which five categories were highest priority for their table and present their choices and reasons to the whole group. Over lunch, responses were collated using a nominal group technique to generate a final list of nine priority categories and these were fed back to the whole group. The small groups were then allocated three priority categories that they had chosen such that each category was independently reviewed by two tables. They were asked to prioritise three questions within each of these categories, present their choices to the whole group and following discussion, group consensus was sought on the three most important questions in each category. The

workshop closed with an open discussion on how the community should take forward research in single ventricle heart conditions. Anonymous feedback cards were provided and individual comments collated.

Results

Stage 1 survey

The initial survey (stage 1) was open from 9th October to 31st December 2017. 128 individuals completed the online form, of whom 49 (38.3%) were adult patients or family members (table 1); patients ranged from 16-24 years to 65+ years. Whilst it is assumed that most respondents were from the UK, responses are known to have been submitted from professionals in continental Europe, North America and Africa.

Respondents posed 340 research questions: 94 with 3 questions, 24 with 2 questions, and 10 with 1 question; on review, four composite questions were split to improve clarity, giving a total of 344 questions. Of these, 271 (78.8%) were classified as *unanswered*, 26 (7.6%) as *already answered*, and 47 (13.7%) as *unable to be answered*. After removing duplicates and rephrasing for clarity and consistency as required, 204 unanswered questions remained which were divided into 20 categories according to emerging themes.

Stage 2 survey

One hundred and fourteen (89.1%) respondents to stage 1 provided an email address and were re-contacted in February 2018. 65 (57.0%) completed the follow-up ranking survey (stage 2), of whom 25 (38.5%) were adult patients or family members (table 1); there was no significant difference between the response rates of patients/family members and healthcare professionals (p=0.85). Nine (13.8%) responses were discarded due to insufficient data or inappropriate completion and 56 (86.2%) were analysed. The scoring of categories and frequency of ranking in the top three are shown in table 2. A full list of the categories and questions taken forward to the workshop is documented in the supplementary material.

Stage 3 workshop

The final stage workshop was held in a meeting venue in central Birmingham, United Kingdom on Monday 23rd April 2018 and attended by 39 participants representing a wide range of perspectives (table 1). An additional 10 adult patients, 5 parents, 12 healthcare professionals and 2 researchers were invited during the iterative process but declined; healthcare professionals from all ten tertiary congenital heart disease programmes in England were invited of which six were represented (see ,list of collaborators). Nine categories were prioritised by at least two tables and taken forward. On discussing the questions in each category, there was a lack of consensus in two categories and it was agreed that more than three questions would be retained as priorities in each. The workshop felt that some questions should be reworded to combine aspects of separate questions. Furthermore, the group felt it was important to broaden the category *Transplantation, mechanical support & stem cell therapy* by renaming it as *Transplantation, mechanical support & novel therapies* as there was apprehension over the unproven role of stem cells, despite much interest from

survey respondents. The final list of 30 research priorities determined by the workshop is shown in table 3.

In the closing discussions, several key themes emerged:

- Collaboration amongst the UK congenital heart disease community, to bring together all centres in a network and establish a working group of key stakeholders;
- Establishment of a national registry for the long-term follow-up of patients with single ventricle heart conditions, learning from the experiences of the Australia and New Zealand Fontan Registry;[12]
- Standardisation of follow-up protocols and recording of a core set of variables to facilitate the registry;
- The importance of continuing to involve patients, their families and charities in these processes [18];
- The need for diverse research methodologies to answer the prioritised questions;
- Engagement with multi-disciplinary researchers, such as engineers, biologists, geneticists, social scientists and industry, and with colleagues across the world through International Fontan Interest Group.[4]

Finally, all patients and parents agreed that their voices had been heard during the workshop and this was supported by individual comments on anonymous feedback cards.

Discussion

Prioritisation of research through consultation with those affected by or caring for those with a disease ensures that it remains directly relevant to improving their lives. In this study, we sought to establish priorities for research in single ventricle heart conditions by engaging with a wide range of stakeholders including adult patients, parents, healthcare professionals, researchers and charities. Through a multi-stage process, we compiled a list of potential questions, filtered out those already answered or unanswerable, removed duplicates, rephrased for clarity and consistency, re-consulted to prioritise questions, convened a diverse group of interested parties and produced a validated final list of priorities. To our knowledge, this study is the first to bring together stakeholder groups to establish specific priorities for research in single ventricle heart conditions and thereby shape the research agenda.

Several studies have assessed research priorities in congenital heart disease including single ventricle heart conditions. Cotts et al for the Alliance for Adult Research in Congenital Cardiology compiled a list of 45 questions and conducted a survey of providers to identify 10 priority questions, with some input from patient groups.[19] Of these, four were specific to patients with single ventricle heart conditions: ‘Is pulmonary vasodilator therapy beneficial in Fontan patients?’, ‘Are warfarin and/or aspirin beneficial in preventing primary thromboembolic events in adult Fontan patients?’, ‘What is the optimal medical therapy for preservation of ventricular systolic and diastolic function in Fontan patients?’ and ‘What is the optimal medical treatment algorithm for Fontan patients with protein-losing enteropathy

(PLE)?', whilst another was also relevant: 'What are the ideal criteria for transplantation referral in ACHD?'. Similar questions to each of these were posed in our initial survey but only preservation of ventricular function was included as a priority. Helm et al conducted an online survey of adult patients, relatives and physicians to prioritise predetermined research topics, including in the Fontan circulation;[20] priorities included the failing Fontan, catheter ablation & rhythm disorders, sex & pregnancy, diagnostic imaging, and quality of life. Finally, McCrindle et al convened a working group to explore issues specific to thrombosis in children, including those with single ventricle heart conditions;[21] despite not including patients or the public in the group, they concluded that patients and their families are important stakeholders in designing successful studies and identified patients with a single ventricle as a priority population for research.

The priorities identified in our study comprise 30 research questions across 9 categories. Several categories which scored highly in the ranking survey (table 2), notably *Outcomes of current treatments*, *Anticoagulation* and *Alternatives to Fontan*, were deemed less important by the workshop participants than some lower ranking categories: *Exercise*, *Brain & neurodevelopment* and *Surgery & perioperative care*. This may reflect specific interests of those attending the workshop or that recognition of the importance of these categories was elevated through the workshop discussions. In addition, *Quality of Life* was felt to significantly overlap with aspects of other categories which ranked higher. The final list of priorities addresses a wide range of issues impacting on those affected by single ventricle heart conditions – from perinatal decision-making to late multi-organ dysfunction, surgical technology to lifestyle choices, and mechanisms of disease to quality of life. Consequently, diverse methodologies will be required to address these questions, including surveys, qualitative studies, translational research and clinical trials, driving collaboration within the congenital heart disease community and across disciplines. Our findings will be publicised nationally, including in charity newsletters and via social media, and we will engage with the National Institute for Health Research, other research funders and National Health Service specialised commissioning to promote awareness of the priorities identified [22].

In this study, we deliberately adopted an approach different to that advocated by the James Lind Alliance to enable us to engage with stakeholders beyond patients, carers and clinicians.[16] We also wanted to generate more than 10 priority questions as single ventricle heart conditions are lifelong, multi-system disorders which impact on patients and their families throughout their lives. Other strengths included: triangulation of the survey and workshop to provide different perspectives, reduce bias and enhance the validity of the findings;[23] engagement with a wide range of healthcare professionals involved in the care of these patients; mixed yet balanced groups on each table to facilitate open discussion, whilst avoiding seating patients or parents with their direct healthcare providers; and obtaining funding to cover travel expenses for patients and parents to attend the workshop. In addition, it provided an opportunity to resolve questions already answered by published research, educate and dispel myths in the wider community.

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Limitations

There were several limitations to this study. Firstly, the mechanisms used to publicise the survey attracted a predominately UK-based audience potentially limiting the international applicability of the questions generated, although there were known to be responses from elsewhere; in addition, the workshop attendees were exclusively living or working in the UK which may have impacted on which categories and research questions were prioritised. The number of adult patients who replied to the initial survey was lower than expected but the response from parents was encouraging. This may have shifted the focus towards paediatric matters, such as diagnosis and surgery, with less attention on later issues, such as longevity and end of life care, although the two highest ranking categories were Fontan failure and transplantation. We invited a range of clinical and research policy makers to participate in the study but none responded, thereby reducing the scope of potential questions regarding resource utilisation and comparative effectiveness. The second stage of the survey was more complex than the first which may have reduced the response rate and the software was not able to adequately enforce the rules for completion, leading to the exclusion of nine incomplete or inappropriate responses. The workshop was held on a weekday to facilitate attendance by healthcare professionals but was seen to impact on the ability of working patients and parents to attend, either directly or through the need for childcare; this may also have skewed the demographic of those present. Furthermore, there was no specific travel funding for professional attendees which may have impacted on how far they were prepared to travel. Finally, our two centres in Birmingham were disproportionately represented at the workshop; whilst we have the largest surgical and adult programmes for the management of these conditions in the UK,[24] the debate could have been unduly influenced by local practices and the final list of priorities has not been externally validated.

Conclusions

We used a multi-stage process to bring together all interested parties to establish a list of priorities for research in single ventricle heart conditions. Our findings provide a platform for clinicians, researchers and funders in the United Kingdom and elsewhere to address the most important questions and drive forward research to improve outcomes in these rare but high-impact congenital heart defects.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Study data were collected and managed using REDCap electronic data capture tools hosted at the University of Birmingham. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for

tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.[17]

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Table 1

Roles of participants in the surveys and workshop.

Role	Initial survey stage 1 (n = 128)	Ranking survey stage 2 (n = 65)	Workshop stage 3 (n = 39)
Adult patients	7	2	4
Patient family members	42	23	5
Parents	38	20	5
Partners	3	3	0
Child	1	0	0
Healthcare professionals	71	34	23
Paediatric Cardiologists	13	6	5
Adult Congenital Cardiologist	9	7	4
Cardiac Surgeons	13	7	7
Cardiac Anaesthetists/Intensivists	9	4	1
Paediatric Nurses	15	5	3
Adult Congenital Nurses	3	2	2
Other *	8	3	1
Researchers	7	5	4
Charity representatives	1	1	3
Policy makers	0	0	0

* Stage 1: 2 Cardiac Physiologists, 2 Cardiac Radiologists, 1 Clinical Perfusionist, 1 Data Analyst, 1 Paediatrician with Expertise in Cardiology, 1 Surgical Care Practitioner. Stage 2: 1 Cardiac Radiologist, 1 Data Analyst, 1 Paediatrician with Expertise in Cardiology. Stage 3: 1 Clinical Geneticist.

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Table 2

Scoring of categories in the ranking survey (stage 2).

Category	Ranking Points	Rank #1 nts	Rank #2	Rank #3	Rank #1-3	Total score	Proceed to workshop
Fontan failure	818	11	10	5	26	1078	Yes
Transplantation, mechanical support & stem cell therapy	658	10	2	5	17	828	Yes
Heart function	713	6	4	0	10	813	Yes
Outcomes of current treatments	691	6	1	5	12	811	Yes
Management of the well-functioning Fontan circulation	666	4	6	3	13	796	Yes
Anticoagulation	646	2	4	5	11	756	Yes
Alternatives to a Fontan circulation	585	3	6	5	14	725	Yes
Associated co-morbidities	649	0	4	3	7	719	Yes
Living with a single ventricle heart condition	638	0	2	4	6	698	Yes
Quality of life	617	4	3	1	8	697	Yes
Arrhythmias	623	3	1	3	7	693	Yes
Exercise	618	0	2	3	5	668	Yes
Brain & neurodevelopment	594	1	1	5	7	664	Yes
Surgery & perioperative care	527	2	2	4	8	607	Yes
Low oxygen saturations / cyanosis	566	1	0	0	1	576	-
Counselling and parental support	518	0	3	1	4	558	-
Liver function	520	0	3	0	3	550	-
Psychological impact	498	2	1	1	4	538	-
Causes of single ventricle heart conditions	488	0	2	3	5	538	-
Pulmonary vascular development & function	451	1	0	1	2	471	-

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Table 3

Final list of research priorities determined by the workshop (stage 3).

Category	Research question
Associated co-morbidities	What are the outcomes in children with multiple co-morbidities?
	What are the common co-morbidities in children with a single ventricle heart condition?
	What is the impact of syndromes or other co-morbidities on the quality of life of those with a single ventricle heart condition and their families?
Brain & neurodevelopment	What factors influence neurodevelopmental outcomes in children with single ventricle heart conditions?
	Are there differences in brain development in the fetus with a single ventricle heart condition and if so, what is the impact on outcomes?
	What is the impact of a single ventricle heart condition on neurodevelopment?
Exercise	What are the effects of regular physical exercise on well-being and long-term outcome in the Fontan circulation?
	What type of exercise is most beneficial in those with a Fontan circulation?
	What are the benefits of exercise rehabilitation in well and deteriorating patients with a Fontan circulation?
Fontan failure	What are the best markers of deterioration in patients with a Fontan circulation?
	What is the main mechanism behind failure of the Fontan circulation?
	How can we prevent late multi-organ dysfunction in the Fontan circulation?
Heart function	What is the cause of ventricular dysfunction in the single ventricle?
	How can ventricular function be best preserved in patients with a single ventricle heart condition?
	What treatments can be developed for ventricular failure in patients with a Fontan circulation?
Living with a single ventricle heart condition	What are the frequencies of symptoms, limitations, physical and emotional quality of life with a Fontan circulation?
	What lifestyle choices (eg. diet, exercise, occupation, physical location) best support the long-term health of patients with a single ventricle heart condition?
	What are the long-term social, psychosocial and other non-clinical outcomes of children with single ventricle heart conditions?
	Which models of care, virtual ward and home monitoring programmes, best support infants, children and young people with a single ventricle heart condition at home?
Management of the well-functioning Fontan circulation	How can the longevity of the Fontan circulation be prolonged?
	How can organ function be optimised in patients with a Fontan circulation?
	What factors best determine a well-functioning Fontan circulation?
	What is the optimal interval for follow-up of patients with a Fontan circulation?
	What is the impact of pregnancy on patients with a Fontan circulation and how can outcomes be improved?

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Category	Research question
Surgery & perioperative care	Which modifiable perioperative factors can reduce mortality for the Norwood operation?
	How can perinatal risk stratification be used to identify those in whom the Norwood operation is futile?
	How could technology be used to perform a biventricular repair in patients with a single ventricle heart condition?
Transplantation, mechanical support & novel therapies	How can mechanical assist devices be developed to support the Fontan circulation?
	What are the roles of novel therapies in the failing Fontan?
	What are the alternatives to transplantation for the failing Fontan?