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Review article

# Design and implementation of multicenter pediatric and congenital studies with cardiovascular magnetic resonance: Big data in smaller bodies

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*Abbreviations:* AHA, American Heart Association; CCRC, Congenital Cardiac Research Collaborative; CMR, Cardiovascular magnetic resonance; DUA/DTA, data use/data transfer agreements; ERM, Experienced Research Mentors; FDA, Food and Drug Administration; FHS, Fetal Heart Society; GDPR, General Data Protection Regulation; HIPAA, Health Insurance Portability and Accountability Act; IRB, Institutional review board; MTA, Material Transfer Agreement; NIH, National Institutes of Health; NHLBI, National Heart, Lung and Blood Institute; PCHD, Pediatric and congenital heart disease; PC4, Pediatric Cardiac Critical Care Consortium; PHI, Protected Health Information; PHTS, Pediatric Heart Transplant Society; RCT, Randomized control trial; PHN, Pediatric Heart Network; SCMR, Society for Cardiovascular Magnetic Resonance; IMMPACT, implementing models for mechanical circulatory presurgical assessment in congenital heart disease treatment; ACTION, advanced cardiac therapies improving outcomes network; ICMR, Indian Council of Medical Research; WHO, World Health Organization; DVD, digital video disc; MTA, materials transfer agreement; IMAGE, international cardiac MRI alliance for cutting edge research in CHD; FORCE, Fontan outcomes registry using CMR examinations; CLARITY, collaboration for longitudinal aortic research in the young; EACVI, European Association for Cardiovascular Imaging; AEPC, Association for European Pediatric and Congenital Cardiology; ASCI, Asian Society for Cardiovascular Imaging; FAIR, findable accessible interoperable reusable; ANCIRR, American College of Radiology national clinical imaging research registry; MACiV, myocarditis after COVID vaccination; PEACE, non-invasive prediction of early cardiac rejection; CERAMIC, CMR evaluation in return to athletics myocarditis screening in COVID-19; PRIISM, pediatric cardiac research initiative in imaging to support mentoring

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ABSTRACT

Cardiovascular magnetic resonance (CMR) has become the reference standard for quantitative and qualitative assessment of ventricular function, blood flow, and myocardial tissue characterization. There is a preponderance of large CMR studies and registries in adults; However, similarly powered studies are lacking for the pediatric and congenital heart disease (PCHD) population. To date, most CMR studies in children are limited to small single or multicenter studies, thereby limiting the conclusions that can be drawn. Within the PCHD CMR community, a collaborative effort has been successfully employed to recognize knowledge gaps with the aim to embolden the development and initiation of high-quality, large-scale multicenter research. In this publication, we highlight the underlying challenges and provide a practical guide toward the development of larger, multicenter initiatives focusing on PCHD populations, which can serve as a model for future multicenter efforts.

## 1. Background

The development and availability of novel surgical and medical interventions for the pediatric and congenital heart disease (PCHD) population has resulted in unprecedented survival within this patient group [1,2]. While survival has improved, questions remain about morbidity and long-term cardiovascular complications within this population. Despite being the most common birth defect (~8 per 1000 births), significant PCHD lesion heterogeneity results in a relatively low incidence for individual lesions [3]. However, small PCHD populations geographically spread across multiple specialized cardiac centers, differences in anatomy and physiology limiting generalizability, practice variability in treatment and monitoring, and regulatory concerns specific to research performed in the pediatric population make high-quality, large-scale research challenging. While there may be benefits to smaller, single center studies, low sample sizes can miss important associations due to underpowering. Furthermore, defining clinical endpoints in the pediatric population can be difficult, as typical endpoints such as death, transplantation, or serious events occur far less frequently than in the adult population.

Various national organizations have addressed these concerns through the establishment of multi-institutional collaboratives to foster large-scale, multicenter research, including the Pediatric Heart Network (PHN) through the National Heart, Lung and Blood Institute (NHLBI), Pediatric Heart Transplant Society (PHTS), Pediatric Cardiac Critical Care Consortium (PC4), Congenital Cardiac Research Collaborative (CCRC), and others within the US and abroad. Within pediatric cardiovascular imaging, multicenter organizations have been developed to similarly foster large-scale, multicenter research. The Fetal Heart Society (FHS) has established an extensive history of high-quality, multicenter fetal heart research, with a worldwide membership of over 500 members and numerous studies in various congenital heart disease populations [4,5]. Within cardiac catheterization, the Congenital Cardiac Research Collaborative (CCRC) includes 17 centers from the US and published nearly 30 high-quality publications focused on improving catheterization outcomes in pediatric and adult patients with congenital heart disease [6]. Cardiovascular magnetic resonance (CMR) is an important tool in the PCHD population for monitoring and follow up, allowing for both an anatomic assessment as well as a quantitative and qualitative assessment of myocardial function, blood flow, and tissue characterization. There is a preponderance of large CMR studies and registries in adults; however, similarly powered studies are lacking for PCHD population. This publication aims to review our experience and provide a practical guide for the development and implementation of effective multicenter pediatric studies (Fig. 1).

## 2. Development of a multicenter CMR study

### 2.1. Establishing a relevant and feasible question

Prior to initiating a multicenter study, three fundamental questions need to be asked (Fig. 2):

1. Is the research question relevant and of significant impact to the PCHD community?
2. Does CMR add value?
3. Is a feasible, multicenter CMR study required to adequately address the research question?

The first question is the most important. Without a clinically relevant and important question, initiating a multicenter study will not be worth the effort and time to pursue. The second question is targeted to the use of CMR in multicenter design, as CMR adds significant costs to a study budget which needs to be well justified by the research design [7,8]. The third question is more nuanced. Rare disease processes with limited cases per individual center will invariably benefit from a multicenter collaboration but there are some important limitations of a multicenter study that must be considered. These will be highlighted and discussed below.

While many important knowledge gaps within PCHD exist, identifying those with the highest impact can be difficult. Within the Society for Cardiovascular Magnetic Resonance (SCMR), a separate 'Knowledge Gap Task Force' was formed to poll SCMR PCHD community members at large and identify collective research goals that were (1) of high

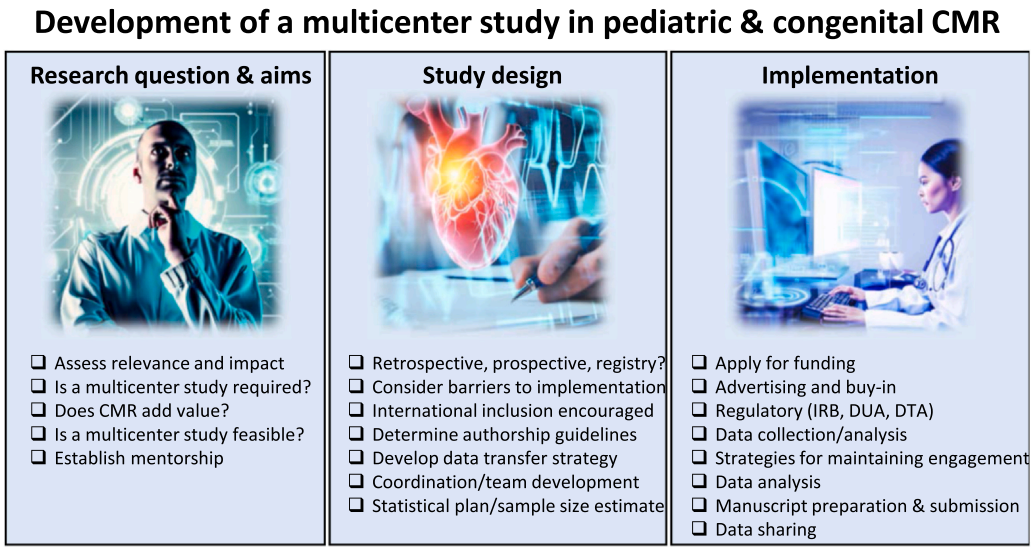


**Fig. 1.** The three phases of multicenter research, including developing research question and aims, study design and development, and study implementation. IRB, institutional review board; DUA, data use agreement; DTA, data transfer agreement

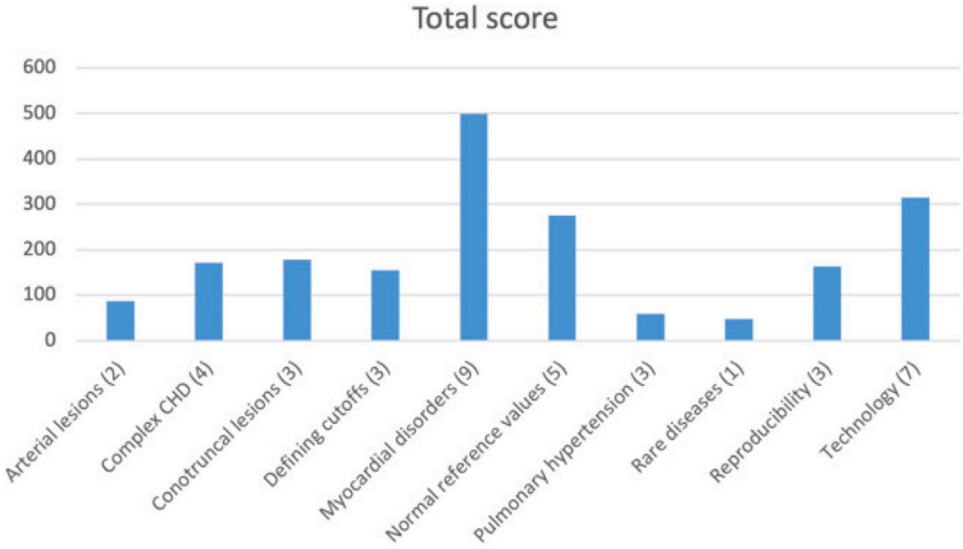


**Fig. 2.** Major recognized PCHD research knowledge gaps, with scores representing degree of priority based on survey responses from physicians and technologists in the PCHD community (with permission from Beroukhim RS "Multicenter research priorities in pediatric CMR: results of a collaborative wiki survey", Sci Rep 2023; 13: 9022).

impact in the field of PCHD CMR, and (2) feasible and answerable from a multicenter study (Fig. 2) [9].

Once a robust research question is identified, internal and external partners should assess the feasibility of a multicenter approach. For the junior investigator, reaching out to more senior colleagues with experience in the study area not only provides appropriate input and strength to the study design, but also presents an opportunity for mentorship. For the more senior investigator, input from others at different institutions will best determine whether the study can generate the appropriate sample size and be accomplished among various CMR vendors and platforms. Starting investigations with smaller, single center studies may provide useful preliminary data and may demonstrate the feasibility of performing a study on a large scale. In order to facilitate multicenter research within the SCMR PCHD community, the Multicenter Collaborative Research subcommittee aims to provide an avenue to facilitate study dissemination among the PCHD CMR community more broadly. Led by senior CMR experts, proposals are reviewed with the intent to help facilitate their execution. Study updates are provided to maintain momentum and enhance recruitment, facilitating the investigator(s) success throughout all stages of a study.

### 2.2. Implementing a multicenter study

Recognition and anticipation of both the regulatory and logistical hurdles to performing a multicenter CMR study helps the investigator to carry out the study efficiently, but also sets expectations for those interested in participating in the study. Regulatory preparation may accelerate the study's progress by implementing effective strategies to overcome these hurdles. Strategies for successfully implementing the multicenter study will depend highly on whether it is carried out prospectively or retrospectively. For this, we review several methods of study design, including retrospective, prospective, and registry.

### 2.3. Retrospective study

Retrospective studies represent an important avenue of research in the field of PCHD CMR. To date, many effective and high-impact multicenter studies utilizing this approach have been employed [10–13]. This approach has numerous benefits (Table 1). Retrospective studies are useful for the study of rare diseases or exposures where there may be an extended period from exposure to outcome [14]. They also

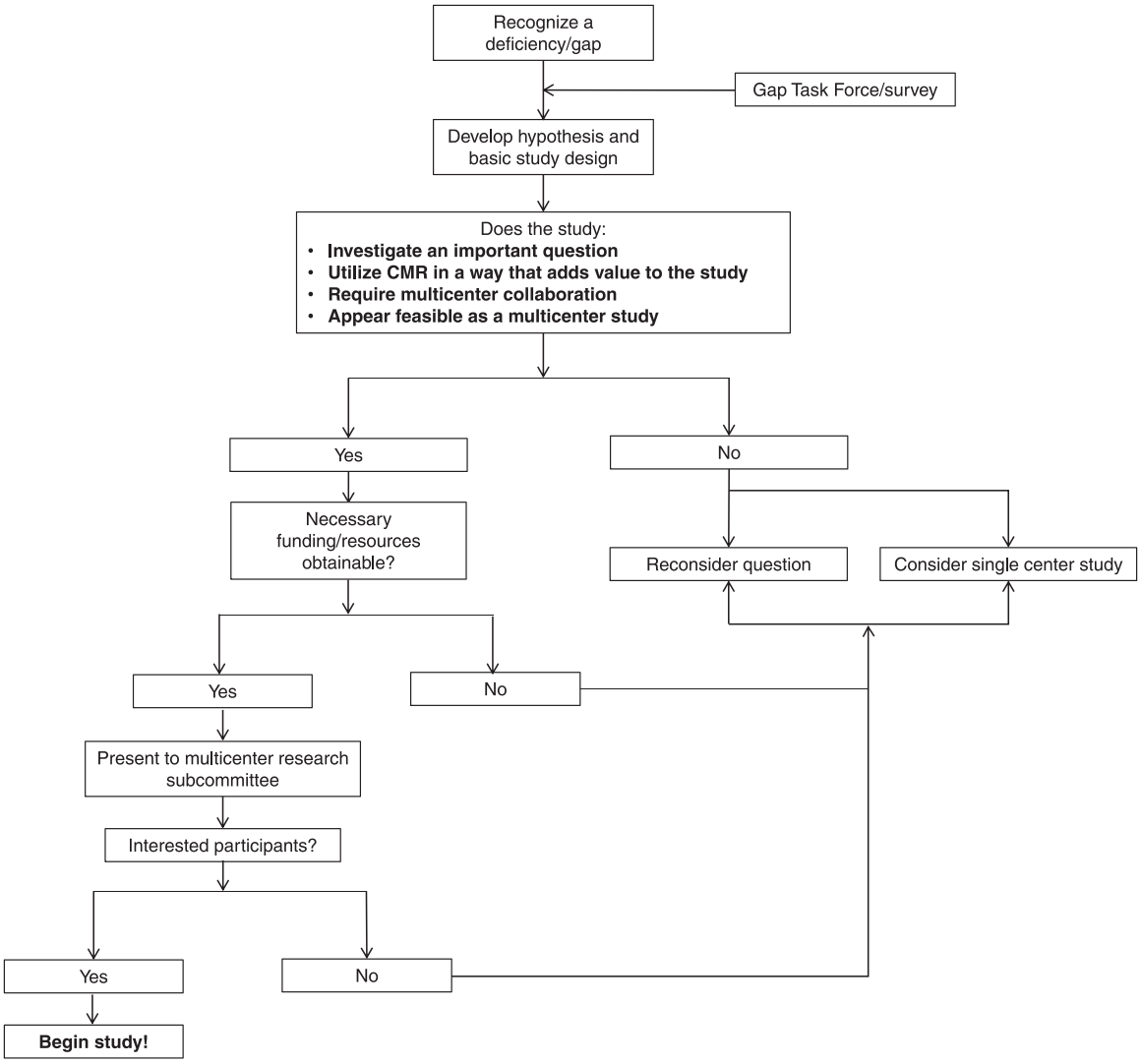


**Fig. 3.** Flow diagram describing process towards developing and performing a multicenter CMR research project.

require significantly less time and funding to complete. From a regulatory standpoint, many Institutional Review Boards (IRBs) allow for waiver of consent and assent, thereby eliminating the need to consent and assent subjects. This waiver also eliminates non-participation biases observed in prospective studies, which may result in over-representation of educated, non-minority, or healthier subjects [15–17]. For these reasons, retrospective multicenter studies are inherently faster to complete and require fewer resources, and are therefore more feasible than prospective multicenter studies.

Despite the benefits of this study design, limitations exist. As retrospective studies are limited to already acquired data, missing data and variations in data acquisition will introduce heterogeneity. The era effect, especially as technology and standard of care adapts over time, must also be considered. Technologic examples include changes in scanner field strength or vendor, variability in sequence parameters (such as field of view, resolution, or slice thickness), and the increasing utilization and modification of novel sequences, such as compressed sensing, parametric mapping, and 4D flow. While potentially subtle, these variations may introduce confounders that can significantly alter outcomes and conclusions. Whereas echocardiography is routinely applied in clinical practice, CMR referral is highly selective among physicians and centers, so selection and referral biases are inherently part

**Table 1**
Potential benefits and challenges of retrospective versus prospective multicenter research studies as they relate to feasibility and impact.

| | Retrospective | Prospective | Registry |
|---|---|---|---|
| Time to completion per patient enrolled | A | D | N/A |
| Feasible with very rare PCHD | A | D | A |
| Feasible with novel/rare CMR sequences | D | A | A |
| Heterogeneity of data | D | A | D |
| Ability to control for CMR scan parameters | D | A | D |
| Likelihood of confounding | D | A | D |
| Cost/Need for funding | A | D | D |
| Resource utilization (coordinator) | A | D | D |

A = advantage, D = disadvantage, N/A = not applicable. *PCHD*, pediatric congenital heart disease; *CMR*, cardiovascular magnetic resonance.

of the vast majority of retrospective CMR studies. Thus, the limitations of retrospectively acquired data may result in a more limited ability to address the question at hand and to generalize the results to current and broad clinical settings. Conversely, data acquired through retrospective studies may be useful for planning and development of prospective studies to address the questions through a more controlled mechanism.

### 2.4. Prospective Study

Prospective study design may present a more controlled approach for studies within pediatric CMR research. Subject identification can be significantly tailored to address the research question at hand. Prospective patient enrollments can minimize missing or unavailable data. Longer enrollment periods may also allow for larger datasets, thereby increasing statistical power and overall impact. Data heterogeneity is inherently less of an issue, as pre-specified scan parameters and data are acquired. Utilization of CMR core laboratories with standardized methods of analysis in prospective studies reduces inter-observer variability as can be observed when multiple centers analyze data [18–20]. A randomized clinical trial (RCT) involves assessment of the effectiveness of an intervention in a prospective study design and remains the gold standard by controlling for the effects of participant characteristics (measured and unmeasured) on the outcome. Few CMR-focused multicenter RCTs exist in PCHD, though some single institution RCTs have been performed [21,22]. Although not primarily focused on a CMR based outcomes, IMMPACT (**I**mplementing **M**odels for **M**echanical Circulatory Support **P**resurgical **A**ssessment in **C**ongenital Heart Disease **T**reatment), is a multicenter RCT investigating the utility of 3D printed cardiac models in pre-surgical planning of ventricular assist devices in patients with CHD[23].

However, prospective multicenter CMR studies also present particular research challenges, mostly related to feasibility, resource utilization, and cost-effectiveness. First, the high cost of CMR examinations significantly increase funding needs [24]. One mitigation for this would be to enroll subjects who are obtaining clinically indicated scans which are billable to patient insurance, but this may come at the expense of further diminished enrollment and selection/referral bias. The complex study design of a prospective multicenter study also requires significant resources beyond image acquisition, including salary support for study coordinator(s) to aid with subject enrollment/data entry/documentation, study subject compensation, image and data transfer, and measures to ensure quality control. These items can contribute significantly to the study budget. Scanner access can also be an issue, as a research scan is being performed in lieu of a clinical exam. CMR examinations are time-consuming and rarely can be performed as point-of-care examinations; therefore, they require significant additional effort and coordination, which may hamper recruitment. Post-processing of CMR data can also be laborious and may result in additional costs. While CMR examinations are generally safe due to the absence of radiation exposure, inclusion of gadolinium contrast administration in prospective studies presents potential regulatory hurdles and may adversely affect subject consent as patients consider risks including IV placement, adverse reactions to contrast, and brain deposition of contrast agents [25]. Furthermore, given likely need for sedation for children under 8–10 years of age, the youngest population is frequently missing or limited in prospective CMR studies and therefore can introduce selection bias.

Despite the advantages of prospective CMR research, some technical challenges persist due to center-level variability in CMR physician expertise/availability. In addition, variability exists for CMR scanner vendor and platform, field strength, and software versions. Even within the same institution, variability in CMR scanner parameters can significantly affect image quality and completeness of all study parameters. For example, T1 mapping values may vary significantly based on vendor, specific scanner, and even temperature [26]. Implementation of controls, such as phantom calibration and standardized post-processing approaches, can help mitigate variability by establishing a correction factor, but may come with additional costs to the study [27,28]. Furthermore, defining imaging protocols to standardize image acquisition (mandating specific field of view, resolution, slice thickness, and contrast dosing) will help reduce variability [29]. Another barrier to broad recruitment of centers may be a paucity of resources critical to prospective and registry research (i.e., clinical research centers, IT infrastructure, legal departments familiar with multicenter data use/data transfer agreements (DUA/DTAs), statistical support, etc.) at smaller centers.

### 2.5. Registry

The distinction between a “study” and a “registry” may at times be subtle. While studies and registries both collect data focused on a particular patient population or PCHD disease state, the use of the data and procedures may vastly differ. Whereas studies require a defined study question, a registry is an observational and frequently open-ended collection system to acquire data that can be used for post-hoc investigation. Registries can also incorporate design elements to roll out a trial “within” a registry, such is the case with other pediatric rare disease registries such as ACTION (**A**dvanced **C**ardiac **T**herapies **I**mproving **O**utcomes **N**etwork) [30]. Development of a registry may present additional regulatory hurdles. For example, given its open-ended nature, typical regulatory limitations on length of data collection or data storage must be adapted accordingly. Furthermore, as there is no “target” enrollment, data storage must accommodate a larger sample size. Regulatory hurdles may exist around data use for future investigators [31]. Finally, as enrollment is ongoing, informed consent may be necessary (discussed below) to continually enroll new cases. If feasible, a registry is a potentially robust mechanism to answer numerous research questions based on a larger sample size than a typical observational study.

Types of patient registries vary greatly, from prospective, longitudinal registries where patient information is updated in real time at set events, to retrospective limited registries, where no protected health information (PHI) is collected. The type of registry created is usually dependent on the type of information captured.

No matter the depth and breadth of a patient registry, the build, roll out, use, and upkeep should be thoroughly conceived before implementation to assure accuracy of the data. Though some patient registries are built solely to capture as much information as possible, most are built on a clear question, albeit big picture versus concrete hypotheses. When designing a study, it is crucial to appreciate the vastness of data points created, keeping in mind those who will be entering data. This is most important when considering a multi-center registry, as “data burnout,” that is, sites having to answer too many complex questions or redundant questions spanning numerous studies, is as real as “study burnout,” when a patient has been inundated with asks to join study after study and refuses all further inquiries.

Data verification is another important consideration for registries. The mechanism in which this is done varies depending on the type of registry. If the registry contains PHI, a data audit can be done in the same way a study would be monitored by the sponsor. If the registry is de-identified, other steps must be taken such as asking a site to re-answer questions on a separate form, or including the screen shot from the medical record where the answer was found, redacting any PHI.

## 3. Study procedures and processes

### 3.1. Ethical considerations and Institutional Review Boards (IRB)

Consistent with the Declaration of Helsinki, research oversight committee approval is necessary for all human subjects’ research worldwide [32]. The extent of regulatory involvement can vary significantly based on the study design, scope of the study, institutional

practice, and individual country. Recognizing potential delays in regulatory approval, especially when including multiple institutions with variable research oversight practices, is an important consideration in the design of a multicenter study. Therefore, it is important to expect that this regulatory phase will require significant investigator time and effort to accomplish- all prior to enrollment of the first study subject. A dedicated team with diverse expertise and passion around the research question is necessary to bring this to fruition.

For some studies in the United States, IRB reliance agreements, or "single" IRB's can be utilized. Under this mechanism, a single institution or independent IRB is delegated to review and approve the IRB submission. All additional sites will then "rely" on the central IRB review and approval to conduct the study [33]. Nonetheless, local IRBs will want to review documents to ensure that local context fits the human research protections at that site. Centralized platforms now exist to standardize and speed up reliance agreements. Use of reliance agreements is required for National Institutes of Health (NIH)-funded multicenter research [34]. Outside of NIH studies, there is significant practice variation, and the use of reliance agreements are generally institution dependent. Whereas some institutions will allow reliance for unfunded studies, others require significant funding or payment to use reliance agreements. Given variability in regulatory practices in different countries, reliance agreements can be difficult for centers outside the United States.

Regulatory differences outside the United States need to also be considered prior to enrolling international centers [35]. In Europe, the General Data Protection Regulation (GDPR), which oversees protection of personal data and privacy for all citizens of European Union nations, has stringent requirements for participation in research, such as prohibition of research with personal data without personal permission, and increased regulations surrounding the transfer of personal data outside of the European Union [36]. Furthermore, the Schrems II judgment declared the European Commission's Privacy Shield Decision invalid, meaning that transfer of personal data from the European Union to the United States or other third countries with insufficient data protection systems is either inadmissible or more difficult. The United Kingdom has retained GDPR as the UK GDPR, alongside the Data Protection Act of 2018. Whereas many United States institutions can obtain waivers of consent or assent, GDPR often requires full consent for all research. Beyond GDPR, individual European Union nations, such as Germany, can interpret regulations differently, and therefore may have stricter regulations that can further make collaboration difficult. In practice, differences between United States and European Union regulations may limit the opportunities to combine data.

Within Asia Pacific, each country has independent rules and regulations regarding IRB approval and data sharing. Most Asian countries have similar standards with regard to IRB approval and decentralized systems for approval. However, approval for clinical trials often requires more centralized review and tends to be longer than in North America; For example, approval in China has been reported to take up to 9 months [37]. Within India, the Indian Council of Medical Research (ICMR) has created standards and guidelines for research approval, mostly allowing individual centers independent authority for IRB approval with the option of a centralized IRB for multicenter research [38]. Though developing countries are frequently underrepresented in multicenter research, variations in practice, resource availability, and staff training make inclusion of centers from some countries challenging [39–41]. Investigators in the US must therefore account for these different policies when enrolling from international centers, as they may further delay site activation. The US Department of Health and Human Services maintains a database of international human research standards of over 100 countries which can be useful in determining specific regulatory procedures for individual nations on every continent [42].

Finally, protection of human subjects often requires partial or complete de-identification of datasets prior to sharing between institutions or a data clearinghouse. It is imperative to set expectations with the IRB and with contributing sites regarding the 22 potential identifiers that may be found within the medical record, many of which are frequently found on the image digital imaging communications in medicine (DICOM) header used in multicenter imaging research. These include patient name, date of birth, age, date of study, medical record number, accession number, and other demographic information such as insurance information, telephone numbers, and address [43].

### 3.2. Study registration

For prospective clinical trials, registration of the trial and its results is an important regulatory step in study implementation. Beyond increasing transparency and reducing bias, registration can be a useful mechanism to recruit patients and referring physicians. The principle of study registration started with the World Medical Association Declaration of Helsinki [32]. Beyond defining ethical principles in performing research, the declaration states that "Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject." The International Committee of Medical Journal Editors has similarly adopted this policy for consideration for publication[44]. Registration has since become common practice, with each jurisdiction having independent methods for study registration, such as clinicaltrials.gov (within the US) and the World Health Organization (WHO) International Clinical Trials Registry Platform (for international studies)[45,46].

### 3.3. Data Use/Data transfer agreements (DUA/DTA)

DUA/DTAs are contractual agreements between two or more institutions that govern the transfer of data between them. These agreements outline the terms and conditions of data transfer, including the direction of transfer (i.e., "sending" and "receiving" institution). Due to concerns about patient privacy and confidentiality, these agreements carefully define the extent of human subject data that is being transferred between institutions. Furthermore, these agreements define the "ownership" of data transferred between these institutions, including what the data may or may not be used for. Usually these agreements are finite in length, beyond which data can no longer be used or agreements need to be renewed. Usually, DUAs are executed by legal representatives at the institutions involved. In some instances, DUAs can be waived for completely de-identified data sets; however, this is dependent on the individual institutions involved. Due to the need for analysis by legal representation at each institution, the execution of a DUA/DTA is frequently the rate-limiting step for center activation.

### 3.4. Mechanisms of data transfer

Before starting a multicenter CMR study, the data to be used and the method of data transfer must be considered. Centralized, cloud-based, privacy- and Health Insurance Portability and Accountability Act (HIPAA)-compliant databases - such as research electronic data capture (REDCap) - are ideal for transfer of clinical information and data. Developed in 2006 at Vanderbilt University, REDCap is now widely available at over 3,000 institutions in 128 countries, and is often provided to investigators at no or minimal cost [47]. Alternative HIPAA compliant cloud-based storage systems are available, though frequently at significant cost for the individual investigator. For studies that involve the use of clinically reported data, without centralized imaging core analysis, utilization of a centralized database is, in most cases, sufficient for data transfer and storage. However, if CMR images need to be processed and analyzed, infrastructural mechanisms need to be in place to transfer the images efficiently and in a HIPAA-compliant manner. If images require de-identification, specialized software will be necessary to remove patient identifiers down to the level of DICOM tags which is offered by most of the available post-processing software vendors. Local radiology/cardiology departments will de-identify

individual studies if DICOM de-identification software is unsuitable or not readily available; the additional costs for this service should be considered when creating the study budget.

Following de-identification, the mode of image transfer must be defined. While digital video disc (DVDs) and encrypted hard drives and thumb drives are an acceptable form of data transfer, shipping costs and potential for data loss and shipping delays must be considered. At present, numerous HIPAA-compliant cloud-based platforms have been developed to facilitate transfer of DICOM images between institutions with guidance available from the US department of Health and Human Services on the use of these technologies [48]. Restrictions on specific vendors and platforms may exist at the institutional level and should be understood before utilizing specific platforms, and employing numerous options in a given study may help minimize delays in data transfer. Investigators may need to communicate with their institutional information systems/information technology groups to facilitate data transfer. Mechanisms to protect data and maintain an organized system for locally storing de-identified data, as well as to define who has access to the data and for what it will be used, is also necessary.

### 3.5. Material transfer agreements

Any study that requires the transfer of non-image materials, such as blood or tissue samples, DNA, etc., will require a materials transfer agreement (MTA). This document is separate from the DUA, which will cover the transfer of images, and the contract for the study. As with DUAs, the configuration can be a simple one-to-one agreement or a more complex agreement, including a consortium agreement that would allow samples from any institution to be transferred to any other institution in the consortium. The setup depends on the needs of the study (a single or multiple core laboratories at one institution vs multiple core laboratories at different institutions), the timing of the study (more complex agreements are time-intensive and may not be optimal if rapid study startup is required), and the long-term goals (planned material sharing across sites may make the upfront time investment more advantageous).

### 3.6. Coordination

Multicenter research can be complex, with specific challenges related to establishing and adhering to regulatory requirements and data transfer needs. As a result, having a well-developed organizational structure to deal with both the regulatory and data aspects is essential (Table 2). Beyond careful record keeping of DUA and IRB approval at individual centers, constant communication between study investigators is necessary. Changes or updates to study procedures or the parameters of DUAs, such as extension of study inclusion/exclusion criteria or expanding study length, will frequently require specific communication to coordinate these changes for all participating institutions. Furthermore, mechanisms to store and protect individual studies and clinical data are required. When CMR images are involved, coding needs to be instituted to ensure images and clinical information are appropriately linked. This is most easily accomplished with a standard nomenclature that allows for separation of data by center and individual subject. While these tasks can be accomplished by the individual investigator, use of research coordinators or staff can offload some of these tasks and free the investigator(s) to complete the study tasks and goals.

### 3.7. Statistical support

Similar to single center research, an established data analysis plan is also necessary to carry out multicenter research, including a power analysis to determine target enrollment and a statistical analysis plan following completion of data collection. While some investigators may have advanced training in statistical analysis and study design, most

**Table 2**
Potential team members and their roles in performing a multicenter study.

| Team member | Role |
|---|---|
| Principal Investigator | • Study design, team development<br>• Elicit interest from other centers, engage external investigators<br>• Secure funding, financial reporting<br>• Maintain communication with external centers<br>• Perform milestone reports/communication with funding agencies and report of study completion<br>• + /- Consent<br>• Analyze data and disseminate through abstracts, manuscripts, presentations |
| Site Investigator | • Manage study at individual site<br>• Point of contact for study principal investigator<br>• Identify subjects for inclusion<br>• Potentially consent, ensure adequate data collection/submission<br>• Participate in manuscript creation and review |
| Legal representative | • Draft contracts for sub awards if study is funded, create DUA/DTA based on study specifications<br>• Coordinate with legal representation from external sites<br>• Elicit signatures from PIs and Directors |
| Coordinator | • Assist with regulatory process (DUA/IRB)<br>• Point of contact for site coordinators/investigators and study participants, answer potential study questions<br>• Enter data/ensure accuracy of entered data<br>• Consent participants<br>• Maintain paper trail (regulatory documents/consents)<br>• Audit data, report adverse events to study PI<br>• Package/shipment of study materials (images, lab samples, etc.) |
| Research nurse (prospective) | • Collect samples, perform vitals<br>• Follow up with patients (clinical information)<br>• report on any adverse events |
| Volunteer/medical student | • Enter and audit data<br>• Review and determine inclusion of potential subjects |
| Data Manager/Statistician | • Aid with study design and grant proposals<br>• Audit data<br>• Perform data analysis<br>• Participate in manuscript development |

DUA, data use agreement; DTA, data transfer agreement; IRB, institutional review board

investigators will require statistical guidance. Many institutions provide free or low-cost statistical consultations for faculty members, and some departments may have dedicated statisticians that can be utilized for analysis. However, if these options are not available, statistical analysis will necessitate funding. As a result, the statistical analysis plan needs to be considered and budgeted, if necessary, prior to undertaking research.

### 3.8. Funding

Given the relatively high professional and technical fees for CMR exams, multicenter prospective research where research CMRs are performed necessitates sufficient funding. In all other cases, funding can be helpful, but may not be absolutely necessary. The NIH is the primary agency of the Unites States government which provides funding via many different types of grants and contracts for medical research. Obtaining NIH funding can be challenging with a long timeline between grant submission, review, and access to funds (Table 3). However, if successful, funds obtained through the NIH can help offset not only study cost, but also administrative and research time to perform the study. Government agencies, such as the Food and Drug Administration (FDA) or Department of Defense, are other US-based funding mechanisms to be considered. Comparable national and European Union related funding opportunities are available in Europe, with similar challenges and rewards.

## 5. Barriers and strategies to successful multicenter study completion

### 5.1. Time

For the clinician-scientist, where clinical and administrative effort is parsed out and clinical productivity is closely tracked, time is often the limiting factor for successful execution and completion of the research study (Table 4). This is especially true in imaging research, where core lab analysis of large datasets of images is a time-consuming process. Financial support can aid in establishing more research time to complete image analysis or cover the costs for hiring core lab staff to process collected data. Furthermore, aside from program support and scanner time, funding should be utilized to pay for critical research staff, such as research coordinators/nurses, project managers, data analysts, statistical support, or even summer students. Personnel salary support allows the principal investigator to delegate the various tasks described thus far, while focusing their time on appropriate management of the study and completion of the study objectives.

**Table 4**
Barriers to performing effective multicenter CMR research and strategies to overcome each barrier.

| Barriers | Strategies |
|---|---|
| Time | • Funding<br>• Research coordinators/image analysts<br>• AI/ML techniques |
| Individual center engagement | • Authorship for participation<br>• Enrollment-based reimbursement of centers<br>• Data sharing for ancillary studies |
| Regulatory hurdles | • Reliance IRB<br>• Consortium/central DUA<br>• MTA (if necessary) |
| Limited enrollment due to rare disease occurrence | • Power calculation<br>• Appropriate inclusion/ exclusion criteria<br>• Streamline study testing |

AI, Artificial Intelligence; ML, Machine Learning; IRB, Institutional Review Board; MTA, Material Transfer Agreement ; DUA, data use agreement

Novel research consortiums and registries can also help to minimize the time for center activation. The SCMR Registry is an example of a highly successful multicenter collaboration that has facilitated several clinically high-impact studies, including The Clinical Impact of Stress CMR Perfusion Imaging in the United States (SPINS) trial, one of the largest multicenter studies in the US to evaluate the prognostic value of stress CMR in patients with stable chest pain [49]. Within the PCHD community, a similar effort is underway with the **I**nternational cardiac **M**RI **A**lliance for cutting-ed**G**e r**E**search in **CHD** (IMAGE CHD), which is an international alliance that is designed to facilitate CMR research by creating an infrastructure to accelerate contracts between participating centers, create an umbrella IRB, and develop a data coordinating center to allow rapid sharing of images and imaging data between institutions. Individual projects can then be developed and initiated quickly with fewer upfront regulatory hurdles.

Finally, innovations in CMR imaging may help to speed up image analysis and therefore increase interest and participation in multicenter research. New machine learning and artificial intelligence systems may result in more rapid analysis when widely available [50]. Federated learning is one example, in which deep learning models are built and trained on individual institution data. This data is then aggregated into

**Table 3**
Types of funding mechanisms and their respective advantages and disadvantages.

| | Advantages | Disadvantages |
|---|---|---|
| NIH/government | • Often larger budget and longer duration of support<br>• Ability to pay for support staff<br>• Frequently renewable (with application) | • Restrictions on centers that can enroll<br>• Strict monitoring/study milestones<br>• Highly competitive<br>• Lengthy turnaround time for review |
| Foundation/Societal | • May be less competitive (depending on society/foundation) | • Specific to disease process<br>• Limited budget and length of funding<br>• Restrictions on use of funds<br>• Restrictions on renewals |
| Industry | • May require limited application<br>• More support for industry product | • High indirect costs<br>• Limited budget and length of funding<br>• Study must involve industry product<br>• Higher academic scrutiny to avoid conflict of interest implications<br>• May not involve salary support |
| Philanthropic | • May be less competitive<br>• Less restrictions on use of funds<br>• Funds may be rapidly available | • Often specific to disease process<br>• Limited budget and duration of funding<br>• Often not renewable<br>• Lower academic visibility |
| Intramural | • Less competitive<br>• High academic visibility within individual center | • Often very limited budget (may be better suited for “pilot data”)<br>• May restrict funding multicenter research/compensate external centers<br>• Often does not involve salary support |

a central server which contains similarly modeled data from other institutions. This has the unique advantage of incorporating training models in a distributed manner, thereby preserving patient privacy [51]. Collection of large robust datasets, such as 4D flow, that allow for retrospective post-processing and analysis may also facilitate retrospective multicenter research studying various aspects of flow on complex CHD.

### 5.2. Authorship

Establishing authorship guidelines is a necessary part of a multicenter study and should be established prior to enrollment of individual centers. Decisions surrounding authorship can not only create tension with site investigators, but can also threaten enrollment and data sharing. Being honest and forthright with authorship expectations at the outset can minimize tension and may help strengthen center engagement and enrollment. Creating trust is essential for the success of a project and is the basis of future collaborations. Regardless of strategy utilized, standards created by the International committee of Medical Journal Editors needs to be followed. These standards include "conception or design, or analysis and interpretation of data; drafting the article or revising it for critically important intellectual content; and final approval of the version to be published [52]."

Within the standards listed above, commonly used authorship strategies are inclusion of one author per participating institution, mentor-mentee authorship in which a senior and junior author per participating center are granted, or metric-based authorship (i.e. determining minimal enrollment to potentially become an author). For manuscripts in which the list of authors is extensive and exceeds the allowed number by a specific journal, a title for the research group may be assigned with author name searchable on PubMed.

### 5.3. Individual center engagement

The hallmark of multicenter studies is establishing engagement from multiple centers around the country and world. While collaboration is widely accepted within the PCHD CMR community, there are challenges to participating in a multicenter study. As discussed above, the regulatory aspects, including obtaining IRB approval and completing DUA agreements, are quite time consuming and can decrease or inhibit momentum. Furthermore, collection of requested data, de-identification, quality assessment, and transfer of images frequently requires use of valuable administrative and research time, and often requires individual centers to use their own research coordinators to help with this process. Participation is frequently delayed due to these hurdles. The need for active participation of collaborating site investigators may be at odds with competing responsibilities (e.g. administrative, clinical, and other research responsibilities).

Numerous strategies can be employed to help maximize site involvement. First, confirmation of authorship on published manuscripts will help ensure that collaborators are scientifically recognized appropriately for their efforts. For studies with the potential for several publications, this can be a significant impetus for participation.

Second, reimbursement and funding can also drive study engagement. Many PCHD CMR studies, including the **F**ontan **O**utcomes **R**egistry using **C**MR **E**xaminations (FORCE), **C**ollaborative for **L**ongitudinal **A**ortic **R**esearch **i**n **t**he **Y**oung (CLARITY), and the Multicenter study on significance of LGE in HCM, reimburse centers for each study subject enrolled, with the potential for higher reimbursement for quicker enrollment. Investigator or research coordinator salary support can also promote engagement of individual centers.

Third, a novel approach to promote collaboration and engagement by centers is through the use of transparent target milestones. For example, FORCE uses a patient enrollment threshold, after which this threshold is met, the Site Investigator is considered as a co-author for all future FORCE related publications. Similarly, after reaching a higher patient enrollment threshold, individual centers can submit proposals to utilize study data and suggest ancillary studies. FORCE has a robust governance process for the review of these proposals with the goals a) to optimize the science and methodology, b) to facilitate collaboration across investigators with similar ideas, and c) to ensure adequate data protection. All of these concepts are also built into the ethical review/IRB and DUA/DTA regulatory documents.

## 6. Additional Considerations

### 6.1. International enrollment

Given the increased global interconnectivity and collaboration on an international scale, enrollment of sites beyond North America and Europe is strongly encouraged. This not only has the potential to increase enrollment but can add racial and ethnic diversity to the study and further expand the generalizability of study results and conclusions. This is especially true for Asian and Pacific Islanders and individuals from developing countries, who are frequently under-represented in US-based studies. Expansion to international centers, though, may result in additional regulatory and funding hurdles. Furthermore, national and regional rules surrounding privacy and data sharing, such as GDPR as discussed above, and significant variability in regulatory staffing and experience, can result in significant delays in site enrollment.

Mechanisms exist to increase international enrollment. Collaboration with international CMR organizations, such as the European Association of Cardiovascular Imaging (EACVI), The Association for European Paediatric and Congenital Cardiology (AEPC) or Asian Society of Cardiovascular Imaging (ASCI) can help increase study visibility and may facilitate center involvement and subject enrollment.

### 6.2. Data sharing and transparency

In an era of increased global connectivity, data sharing and accountability has taken greater precedence. In 2016, a consortium of scientists and organizations introduced the concept of FAIR (Findable, Accessible, Interoperable, and Reusable) Data Principles as a set of guiding principles for advancing the reusability of digital data [53]. Proposed mechanisms for data sharing include supplementary or metadata with publication or cloud-based databases to share available data with interested investigators.

The FAIR principles present unique challenges in the world of CMR research. While a cloud-based approach may work well for databases, image repositories require significantly more storage capacity and can be cost prohibitive. Furthermore, DUAs are often prohibitive for sharing DICOM or individual subject-level data. However, some unique initiatives may help combat these hurdles.

Image registries are an ideal mechanism to promote data sharing and accessibility. The SCMR Registry is an imaging repository that allows individual centers to upload de-identified patient data and images that can then be available to the broader CMR community. Currently, over 74,000 cases are available and searchable by clinical or imaging-based criteria [54]. Research studies using registry data can be proposed, and if accepted, images and clinical data downloaded to allow secondary analysis. As infrastructure for this mechanism is costly, nominal fees are involved to contribute and participate in this registry. Image repositories are available in other imaging modalities, including echocardiography (ImageGuideRegistry [55]), and numerous image modalities through the American College of Radiology (ACR National clinical Imaging Research Registry (ANCIRR) [56]).

Metric-based data sharing is an alternative mechanism to support data transparency and availability. As discussed above, in addition to providing compensation for each individual contribution, the FORCE registry allows access to data and proposal of ancillary Fontan studies

should an individual center contribute a pre-specified number of studies. This mechanism promotes increased contribution of FORCE data from individual centers while maintaining FAIR principles in research. A similar model could be envisioned for other PCHD CMR research.

Finally, creation of unique consortia, such as IMAGE CHD, with umbrella DUAs and IRBs can also promote data sharing. The time-consuming regulatory limitations of creating IRBs and DUAs for individual studies are replaced by an all-encompassing agreement that allows for rapid distribution of images and clinical data to all participating centers.

### 6.3. Collaborative research partnerships and Mentorships

Research partnerships between experienced investigators at different institutions with varied research interests, skillsets, and collaborative networks but with a common question can result into successfully funded multicenter studies. The **M**yocarditis **A**fter **C**OVi**D** **V**accination (MACiV) study is one such example of collaborative research partnership[13]. Being actively involved in various national and international professional organizations leads to expansion of a network of colleagues which can eventually help in initiating a multi-center study.

The other way to build multicenter studies is via mentorships. The SCMR PCHD Multicenter Collaborative Research subcommittee, as well as the PCMR and SCMR Early Career subcommittees provide mechanisms for junior investigators to network with senior members at other institutions, thereby promoting collaboration and development of novel studies or research ideas. Numerous studies in PCHD, including Non-invasive **P**rediction of **Ea**rly **C**ardiac r**E**jection (PEACE), Normal ECV values in children, and **C**MR **E**valuation in **R**eturn to **A**thletics **M**yocarditis screening **I**n **C**OVID-19 (CERAMIC), were conceived and implemented via this framework.

Fellow and junior faculty involvement in multicenter research is encouraged wherever possible. For the junior investigator, research participation provides an opportunity to network with senior faculty within their institution as well as with senior investigators at other institutions. Optimally, through these forums, faculty will grow in their research expertise, ultimately developing and performing ancillary studies as first author, thereby expanding their research portfolio and advancing the field. Furthermore, inclusion of junior faculty can increase their expertise through authorship, protocol development, and grant writing, all of which aids their individual career development. Because the timeline for multicenter research is typically longer than the standard 1-year cardiac imaging fellowship, fellows are typically encouraged to contribute to multicenter research as the first step in becoming a part of the collaborative network rather than to lead studies from the outset.

Limitations in the availability of NIH- or grant-funded research mentors in the PCHD imaging community led to the development of **P**ediatric Cardiac **R**esearch **I**nitiative in **I**maging to **S**upport **M**entoring (PRIISM)[57]. The goal of this initiative is to connect junior investigators in pediatric cardiac imaging interested in developing an investigation-focused academic career to a diverse network of seasoned senior PCHD investigators. In this research collaborative, junior investigators can submit potential research grants for review by a panel of Experienced Research Mentors (ERMs) to maximize the likelihood of successful funding. Additional planned initiatives of this program include seed grants as well as annual educational conferences and webinars.

## 7. Conclusions

Due to disease rarity, conducting PCHD CMR research necessitates multicenter collaboration to study research questions in this field. As technical advances are made for CMR hardware and software, PCHD providers bring their expertise to bear. The establishment of the SCMR multicenter research subcommittee has helped to build trust, to guide research protocol development, and to successfully complete many PCHD studies, bringing these innovative imaging techniques to the PCHD population. Now, with knowledge of the challenges, CMR researchers have shared strategies to move forward with multicenter research collaborations and to harness the power of big data.

Grants through cardiology and imaging societies are alternative mechanisms through which to obtain funding. Examples of such societies include the American Heart Association (AHA) (US),European Society of Cardiology and the Association for European Paediatric and Congenital Cardiology (Europe), African Research Excellence Fund (Africa), or the Asia Pacific Society of Cardiology (East Asia, Asia-Pacific, Australia, and the Middle East. However, these societies often provide significantly less funding than many of the NIH grant mechanisms. Foundations and societies focused on individual disease processes, such as the Muscular Dystrophy Association, the Marfan Foundation, Pulmonary Hypertension Association, or Children's Cardiomyopathy Foundation, have funding mechanisms that often can help offset the costs of prospective CMR research and can also generate early results that can lead to successful applications to larger grants. Private philanthropy can also be a powerful mechanism for research funding, and often results in fewer restrictions on use of funds. However, this mechanism may result in a more limited budget and is often not renewable. Intramural funding from an investigator's local institution is another potential source of funding, although it can be challenging to fully support a multicenter study. Using a stepwise approach, intramural funding may generate pilot data that can subsequently be used for extramural funding applications.

Private industry support is an alternative mechanism for funding of CMR research. CMR vendor funding can be explored for financial support or partnership, with the benefit of potentially expanding involvement to international centers.

Aside from discrete monetary funding, research support can come in other forms. Software vendors are becoming a valuable resource towards advancing CMR research. Considering the expanded landscape of available software platforms, partnering with a software vendor can provide a mutually beneficial arrangement that has the potential to significantly enhance a research study. While many do not provide monetary funds, complementary or reduced-cost software licenses can significantly advance research studies with novel technology and may help save available financial resources to fund other parts of the study, such as ancillary support or analysis/scanner time.

## Ethics approval and consent to participate

Not applicable.

## CRediT authorship contribution statement

**Rebecca S Beroukhim:** Writing – original draft, Supervision, Methodology, Formal analysis, Conceptualization, Writing – review & editing. **Margaret M Samyn:** Writing – review & editing, Writing – original draft. **Lars Grosse-Wortmann:** Writing – review & editing, Writing – original draft. **Supriya S. Jain:** Writing – review & editing, Writing – original draft. **Jonathan H Soslow:** Writing – original draft, Writing – review & editing. **Kanwal M Farooqi:** Writing – review & editing, Writing – original draft. **Shaine A Morris:** Writing – original draft, Writing – review & editing. **Francesca Raimondi:** Writing – review & editing, Writing – original draft. **Brian M Fonseca:** Writing – original draft, Writing – review & editing. **Timothy C Slesnick:** Writing – review & editing, Writing – original draft. **Rahul H Rathod:** Writing – review & editing, Writing – original draft. **Simon Lee:** Conceptualization, Writing – original draft, Writing – review & editing. **Colin J McMahon:** Writing – original draft, Writing – review & editing. **Michael P Dilorenzo:** Writing – review & editing, Writing – original draft, Resources, Methodology, Data curation, Conceptualization.

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