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Prevention of Sudden Cardiac Death in the Young: Developing a Rational, Reliable, and Sustainable National Health Care Resource. A Report from the Cardiac Safety Research Consortium

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ABSTRACT

This White Paper, prepared by members of the Cardiac Safety Research Consortium (CSRC), discusses important issues regarding sudden cardiac death in the young (SCDY), a problem that does not discriminate by gender, race, ethnicity, education, socioeconomic level, or athletic status. The occurrence of SCDY has devastating impact on families and communities. SCDY is a matter of national and international public health and its prevention has generated deep interest from multiple stakeholders, including families who have lost children, advocacy groups, academicians, regulators, and the medical industry. To promote scientific and clinical discussion of SCDY prevention and to germinate future initiatives to move this field forward, a CSRC-sponsored Think Tank was held on 21st February 2015 at the United States Food and Drug Administration's White Oak facilities, Silver Spring, MD. The ultimate goal of the Think Tank was to spark initiatives that lead to the development of a rational, reliable, and sustainable national healthcare resource focused on SCDY prevention. This paper provides a detailed summary of discussions at the Think Tank and descriptions of related multi-stakeholder initiatives now underway: it does not represent regulatory guidance.

INTRODUCTION

A Think Tank sponsored by the Cardiac Safety Research Consortium [1] was convened at the United States (US) Food and Drug Administration (FDA) Headquarters Silver Spring, Maryland, on 21st February 2015 to develop consensus around improving current efforts to detect young individuals who unknowingly have conditions that could result in sudden cardiac death. Sudden cardiac death in the young (SCDY) spans age, gender, race, ethnicity, education, socioeconomic class, and levels of participation in exercise. It is a matter of national and international public health concern involving families who have lost children, advocacy groups, academicians, regulators, and manufacturers of both diagnostic and therapeutic medical products. Unlike other countries including Japan, Italy, and Israel, the United States has never supported a national program for early detection of diseases that cause SCDY. While there is agreement that SCDY needs to be addressed, there has been a lack of consensus among clinicians and academicians as to the methods of disease screening that provide optimal sensitivity and specificity minimizing both false positives and false negatives. This lack of consensus has resulted in a complex landscape with multiple prevention and screening programs led by public groups ongoing in the midst of occasionally contentious debate over best practices for cardiac screening of generally healthy young.

Based on the principles of the FDA Critical Path Initiative, the CSRC was created in 2006 to facilitate collaborations among academicians, industry professionals, and regulators to develop consensus approaches addressing cardiac and vascular safety issues that arise in the development of new medical products [2]. The CSRC's previous focus on cardiac safety related to novel therapeutics in pediatric populations[3] was expanded for the purposes of this Think Tank, leveraging the CSRC's long history of enabling collaboration in the face of challenging cardiac safety regulatory and public health issues. Under the general principles and leadership of the CSRC, engaged stakeholders were brought together to address the development of a more structured national approach to screening processes and data collection that could enhance both the predictive interpretability of screening efforts for SCDY and other public health concerns related to predominantly "normal" pediatric populations. The ultimate goal of the CSRC Think Tank was to generate consensus on pragmatic steps to develop a more rational, reliable, and sustainable national healthcare resource that leverages current screening efforts while enhancing the quality of predictive information addressing this problem.

This paper presents a detailed summary of discussions at the Think Tank by a broad range of experts, now further extended by the CSRC writing group, as well as an update of subsequent initiatives and work streams resulting from this meeting. The CSRC views expressed herein do not represent regulatory policy.

THE STAKEHOLDERS

SCDY is devastating and has widespread, powerful effects on our entire population. In some, passion and energy to prevent SCDY is manifest as advocacy and action that impacts the public sector at the individual, community, and state levels. In others, the approach to the problem is scientific, academic, or rooted in technology. As such, the stakeholders with interest in addressing SCDY are as diverse as the affected population. Each stakeholder group has unique viewpoints on how to approach the detection and prevention of SCDY, but all agree that: 1) efforts at prevention are crucial, and 2) there is ample opportunity to improve on the yield of such efforts relative to the current national landscape. While all input, summarized here, is valuable, attainment of the goal of developing a rational, reliable, and sustainable national healthcare resource was driven primarily by the CSRC processes focused on developing consensus around priority objectives and pragmatic steps forward.

Parents, Family and the General Public

In addition to the young who suffer, and occasionally survive, sudden cardiac arrest (SCA) the stakeholders who are impacted the most are the parents, siblings, and other family members whose child, sister, or brother died suddenly and unexpectedly. As a result of SCDY and SCA events, many families have established non-profit foundations or other organizations committed to raising awareness and to supporting screening for risk of SCDY in local populations. Beyond parents and families, the sudden death of a young individual may affect broader communities made aware of the loss through media reports. The local public reporting of a sudden death event may be followed by grass-roots screening events. Currently the reliability or efficacy of these screening events for SCDY prevention is unclear. Nonetheless, the resultant public awareness may have indirect effects on reduction of SCDY that are not easily quantified. Public groups with SCDY interest include sport-related agencies at the collegiate (NCAA) and professional

level, and those that involve younger athletes, e.g., schools with high school teams and club sports. Recently the NCAA issued updated recommendations on screening for cardiovascular safety [4].

Academia

Interest and involvement in the issue of SCDY in the medical community ranges from individual healthcare providers assisting and/or initiating screening events locally to involvement recommendations on screening efforts by the major national medical societies. At the society level, the American College of Cardiology (ACC), American Heart Association (AHA), Pediatric and Congenital Electrophysiology Society (PACES), Heart Rhythm Society (HRS), the American Academy of Pediatrics (AAP), the American Medical Society for Sports Medicine, and the American College of Sports Medicine, as well as other groups in sports medicine, have subgroups/committees related to pediatric and congenital cardiovascular diseases that consider screening methods. Medical providers typically belong to several academic societies and are members of multiple subcommittees. Given that the population of interest is children and young adults and that most subgroups are members of societies with primary interest related to the adult population - with the exception of AAP, PACES, and sports medicine groups that advocate for adult and pediatric populations — the commitment of the overall medical societies to this area is evolving, and several academic groups have published recommendations for content and technology use related to screening for SCDY [5, 6].

Regulatory Agencies

Direct involvement of the regulatory arm of the US government on the issue of sudden cardiac death in pediatric age-groups has been primarily focused in the area of drug safety. Regulatory bodies participating on The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) are indirectly and deeply involved in prevention of SCDY by virtue of regulatory guidelines requiring premarket evaluation of medications for QT-prolonging effects[7, 8]. The basis for these regulatory guidelines comes from concern for agents causing fatality from drug-induced QT prolongation causing ventricular arrhythmias [9, 10]. However, similar to SCDY, the actual incidence of this problem is unclear. It is also unclear if issues related to drug-induced QT prolongation are relevant only in susceptible individuals, (e.g.,

those with undiagnosed subclinical genetic mutations of cardiac ion channels) or may affect other individuals. Furthermore, while the definition of ‘normal’ for these purposes may be clear in an adult population, normative data accurately characterizing the influence of age, gender, and ethnicity in an actively developing pediatric population are absent. As such, setting a definition of ‘abnormal’ as a safety-signal is difficult and the extent to which efforts to assess QT prolongation by medications has led, or will lead, to prevention of SCDY is not clear, despite extensive resources having been committed to this effort.

Industry

Manufacturers of both diagnostic and therapeutic devices may have a significant interest in this issue beyond humanitarian and public health interest. Significant opportunities may exist for improving diagnostic technology. The expansion of cardiac screening efforts across the population could represent a significant business opportunity for manufacturers of both diagnostic (i.e. ECG) and therapeutic (i.e. defibrillator) devices. The pharmaceutical industry already has a substantial financial interest in the area of QT evaluation in pediatric populations exposed to pharmaceuticals. As noted, the premarket strategy for evaluation of compounds for QT prolonging effects is articulated by international regulatory guidelines for adults, however, compounds are not routinely evaluated in either “normal” or vulnerable pediatric populations. New scientific information that affects the ability to enhance safety or helps increase the efficiency of drug evaluation for pediatric populations could have a major impact on this industry.

DISCUSSIONS AT THE THINK TANK

Representative stakeholders from many of the areas outlined above participated in discussions related to SCDY. The segments below summarize discussions aimed to articulate the problem, evaluate the current state, and develop goals for future progress. Slides from individual talks are accessible at the CSRC website[1]

Grass Roots Screening Fueled by Passion: The death of a child at any age is devastating to parents and family. Sharon Bates, the mother of Anthony Bates, discussed her son’s life, the

impact of his sudden death, and her efforts related to founding the Anthony Bates Foundation and to maintaining its ongoing cardiac screening activities. Anthony Bates played on sports teams starting at five years of age. Throughout his life, he had numerous sports physical examinations. He had no symptoms. He had no family history of heart problems or sudden death. He appeared healthy and active without limitations. He was recruited to play football in the NCAA. In July 2000, after a light workout at Kansas State University, he died suddenly, without warning. It was discovered post-mortem that Anthony died from Hypertrophic Cardiomyopathy (HCM).

Anthony Bates' death prompted Sharon Bates to dedicate her life to help other families avoid that same experience. With donations and her own resources, she created The Anthony Bates Foundation (ABF, www.AnthonyBates.org) to raise awareness of SCDY and champion its prevention. In 2005, Sharon Bates, and three other mothers who each lost a child due to an undetected heart condition founded Parent Heart Watch (PHW, www.ParentHeartWatch.org). PHW was established as an action-driven group to bring awareness of risk factors for SCDY and to provide education and advocacy on primary and secondary strategies for prevention of sudden death. PHW provides cardiopulmonary resuscitation (CPR) and automated external defibrillators (AED) training, facilitates creation of cardiac emergency response plans and promotes AED accessibility. In addition to ABF and PHW, many other public screening foundations and organizations are active in the United States and perform regular screening events with large numbers of participating individuals.

Scientific Underpinnings of SCDY: The incidence of SCDY is variably reported and in the range of 0.5 to 8 per 100,000 person-years[5, 6, 11], but the true incidence is unknown. The most common causes of SCDY include rare congenital conditions – genetic or anatomic problems which are present from the time of cardiac embryogenesis – and include Hypertrophic Cardiomyopathy (HCM), genetic arrhythmia syndromes (Long QT Syndrome [LQTS], Catecholaminergic Polymorphic Ventricular Tachycardia [CPVT], Brugada Syndrome [BrS], Arrhythmogenic Right Ventricular Cardiomyopathy [ARVC]), congenital abnormalities of the coronary arteries or cardiac valves, Wolff Parkinson White Syndrome (WPW), Marfan Syndrome, and others. SCDY can also occur in the setting of acquired cardiac conditions such as myocarditis and, in rare circumstances, coronary artery disease (though typically seen in older

adults). In the case of congenital diseases, the condition develops in utero as a result of either a spontaneous or inherited genetic mutation. However, while the genetic mutation may be present from birth, the development of actual disease may be age-related, may take years to become manifest, or may not be significantly expressed. Additionally, even after the cardiac condition manifests, the actual risk of SCD is unknown. A child with a mutation associated with LQTS, for example, may have arrhythmia and sudden death as an infant while another child may not experience arrhythmia until adolescence or older. Therefore, multiple challenges exist not only in disease detection but in stratifying individual risk. These two areas are central to many controversies surrounding prevention of SCDY. Given the unpredictable nature of events in these diseases and the resultant difficulties in assessing risk, much attention has been focused on detection (screening) in potential ‘at-risk’ populations, such as athletes, (a group with presumed higher risk related to activity), with the underlying assumption that detection will enable prevention. Furthermore, reliable data on drug exposures and “off-target” cardiac toxicity effects is not available to help understand to what degree other molecular mechanisms may play a role in triggering SCDY events in susceptible individuals.

The public health nature of this problem and the issue of screening populations have not gone un-noticed. These were studied and evaluated by a national NIH/NHLBI working group and reported in 2011.[5] After careful evaluation of the evidence, the working group concluded with multiple recommendations as noted below:

- 1) Epidemiology and etiology of Sudden Cardiac Death in the Young (SCDY)
 - a. Develop a SCDY registry to prospectively estimate the incidence of SCDY
 - b. Perform case-control studies using registry-defined cases to identify risk factors for SCDY
- 2) Performance of the screening methodology in the target population
 - a. Perform pilot ECG screening studies to test the characteristics of the ECG in target populations
 - b. Perform comparative effectiveness studies to determine the incremental value of various screening methodologies, including history and physical examination, ECG, echocardiogram, and genetic testing
- 3) Management of asymptomatic heart disease identified by ECG screening
 - a. Develop evidence-based management strategies for asymptomatic patients

- b. Evaluate risk stratification, prevention, and therapeutic strategies
 - c. Use novel study designs and innovative recruitment strategies when studying low-prevalence diseases
- 4) Impact of a screening program
- a. Evaluate the impact of a screening program on individuals and families using quality-of-life studies and patient-preference measurements
 - b. Use decision analysis to evaluate overall effectiveness of a screening program, as well as cost and resource utilization

It was recognized that assessment of the ability to prevent SCDY in part depends on accuracy of sudden death reporting across the US. To address this problem, the NIH/NHLBI is sponsoring the Sudden Death in the Young (SDY) Initiative[12]. The goals of this initiative are to establish the incidence of SCDY in the United States and to investigate etiologies and risk factors for SCDY. The initiative is currently in Phase II of the trial. Phase I focused on development of a surveillance system to identify cases, creation of a registry of clinical information about each case based on death certificates, medical records, death scene investigations, pathology reports, and biospecimens from each case for further evaluation of potential genetic etiologies of the death. In Phase II, the registry data will be made available to investigators in the scientific community and there will be support for mechanistic, genetic, and other studies that use the registry to evaluate causes of and risk factors for SCDY.

The detailed evaluation of the NIH/NHLBI working group and the SDY Initiative demonstrate the overall importance of this area as a challenging and high priority national problem and provide identification of key areas that need to be addressed.

Global Perspective on Screening for Sudden Cardiac Death

SCDY is an international problem shared across cultures. As such, the issue of screening has been discussed in many countries. Japan, Italy, and Israel have government-mandated screening programs that have yielded conflicting results. In Italy, pre-participation screening has

been shown to reduce SCD[13]. However, it is unclear whether this success reflects some degree of study bias given the specifics of the population studied[14].

Japan initiated cardiac screening in 1954, and school-based heart screening was mandated in 1973. In 1994, school-based ECG screening was mandated for 1st, 7th, and 10th grade children. The screening process in Japan includes history, physical examination by school doctors, and 12 or 4-lead ECG interpreted by pediatric cardiologists. Abnormal ECG, history of Kawasaki Disease, or symptoms are detected in less than 5% of screened children and are considered indicators which warrant further investigation. Secondary screening includes physical examination performed by pediatric cardiologists and other tests such as an echocardiogram. This may lead to a ‘third step’ that involves diagnosis of disease severity and structured management including limiting certain levels of physical activity. The school-based screening program in Japan has been considered to be useful and cost-effective for detecting high-risk subjects, as following the onset of screening, a significant drop in mortality rate in Japan in these age groups has been reported [15].

The Japan experience is in contrast to that in Israel where mandated screening of athletes was initiated in 1997. The mandate includes yearly history and physical exam, ECG screening, and exercise testing every one to four years. Despite this program, a comparison of SCDY death rates in the twelve years prior to and twelve years following the onset of screening, using newspaper/media reports for data, did not demonstrate any significant changes in SCD rate[14].

Screening

Despite the NIH/NHLBI recommendations to determine the impact of a screening program, the issue of optimal screening methods and overall effectiveness for prevention in SCDY individuals has been actively debated in the US. At the academic, scientific, and public health levels, there are strong arguments over concerns about use of technology, false positives, false negatives, cost-effectiveness, quality, and variability across relevant risk conditions (HCM, long QT, anomalous coronary, etc.), with much debate based on limited data.

At the public level, it is clear that many groups have already made the decision to proceed with screening for individuals at high risk for SCDY. Many groups, organized as foundations or as impromptu associations, currently conduct public screening events. There is a significant

range of organization, training, and technology across these groups. Some groups have advanced corporate structure with private funding, advanced event organization, and sophisticated data collection. Many groups have support or collaboration from local community, from industry and from medical professionals. The support and collaboration of medical professionals range from voluntary interpretation of data to full Advisory Board-level involvement and evidence-based guidance.

The grass-roots origins of the screening groups, geographic separation between group sites, and differences of focus on SCDY etiologies have resulted in significant disparities in the performance of cardiac screening. Groups started by families who have lost children due to SCDY have substantial motivation, energy, and commitment. These groups are motivated both by general concerns about public health as well as personal interest in preventing a repeat of the tragedy that occurred in their own family. However, many groups lack sufficient funding to adopt sophisticated screening practices, proceeding nonetheless with performing limited assessments, data storage, and scope. Some groups have obtained additional funding from private and/or industry sources, and have subsequently expanded their screening efforts. Previous efforts to organize and unify screening events between groups have had little impact and there remains disparity and lack of agreement related to the most effective methods of screening.

Despite lack of scientific data confirming effectiveness of public screening performed in any manner, public screening groups feel that what they currently do is making a difference. The lack of consensus or action on the part of the medical community or advancement of science in the area of SCDY has frustrated but not dissuaded this public effort. The extent to which public effort has bypassed the medical community is perhaps expressed by pending laws in several state legislatures related to athletic screening. The establishment of screening legislation without consensus oversight or agreement as to best practices could result in further regional differences in screening practices that will make pooling of data and scientific evaluation of the effectiveness of screening extremely difficult.

Screening Effectiveness

Cardiac screening differs from cardiac *diagnosis*. A ‘screen’ is performed to identify an individual who *may* have a condition known to be associated with SCDY and, therefore, *may*

need detailed medical evaluation to determine (1) if there is a condition present and (2) to determine or evaluate the degree of risk of SCDY and counsel and/or treat the individual appropriately.

Therefore, screening is performed to gather information, but the extent of information to obtain for optimal and effective screening is not clear. Information that has traditionally been obtained includes, but is not limited to, personal history, physical examination findings, elements of family history, electrocardiographic (ECG) data, and echocardiography data.

There are multiple challenges to screening for risk of SCD. The frequency of SCD is low, and the diseases associated with SCD are heterogeneous. The manifestation of some of these diseases changes with age, as does the risk of SCD. While there has been much focus on death in athletes, sudden death can also occur in non-athletes and, in either group, SCD may occur during periods of non-exertion. Ideally, optimal screening methods would use appropriately matched “normal” criteria for the population being screened to minimize false positive or false negative results. However, these matched criteria do not currently exist to allow risk stratification in the young by age, ethnicity, gender, activity level, etc.

Other challenges include the variable quality of data being obtained across screening efforts. Currently, data obtained by history may vary extensively. The data obtained for family history are not standardized and reported symptoms in adolescents may be ambiguous. A physical examination for screening may mean very different things to people who perform it and may be performed by individuals with widely varying medical backgrounds. Additionally, while it may be assumed by many that a medical test, such as an electrocardiogram (ECG), yields a definitive conclusion, the interpretation of an ECG varies even among experts. In part, this variability in ECG interpretation arises because “normal” ECG interval measurements and morphologic findings vary by age, gender, race, ethnicity, physical conditioning, body shape, and weight. Indeed, normal ECG values across heterogeneous pediatric populations are not well established. Further complicating screening is that some common causes of SCDY, such as the presence of a congenital coronary artery anomaly, are virtually undetectable by ECG.

An ideal screening test has high sensitivity and specificity with low rates of false negatives (missing a person at risk) and low false positives (declaring a healthy person to be at risk). In cardiac screening in pediatric populations, the personal history component is relatively insensitive to identifying most conditions that may cause SCDY. In the best of studies, the

sensitivity of personal history (i.e., detecting the true positives) is less than 50%, and may be less than 10%. There are also many false negatives because an individual with one of the conditions that cause SCDY may be completely asymptomatic until a sudden death event occurs. Further complicating the personal history data is an overlap between symptoms such as dizziness or palpitations, which are commonly reported in adolescents, but which may also indicate increased risk of SCD. Therefore, with a personal history alone, these individuals may be incorrectly identified as abnormal and at risk.

Family history information may be valuable. In a population study by Corrado et al [13], in 11% of cases of SCD, there was a positive family history of SCD or cardiomyopathy. In another study of sudden death in the young [16], out of 240 SCD, there was a history of SCD in a first-degree relative in 4.5%. Therefore, while the inclusion of family history in screening can increase sensitivity, it is time consuming and the questions posed may have to be customized on the basis of region and ethnicity. Unfortunately, many family members are unfamiliar with their own family history and many with SCD are labeled as having a heart attack.

The physical exam has limited utility in screening for SCDY. Among the major conditions that can lead to SCDY (HCM, WPW, LQTS, CPVT, ARVC, congenital coronary anomalies), the physical exam would potentially be useful only for detection of HCM. Studies have shown that the issue of false positives can be significant when screening with history and physical examination with false positive rates of 15% for physical alone and 22% for history up to 30% for H&P together[17].

Studies published related to added value of ECG screening demonstrate sensitivities up to 67 to 100% for detecting cardiac disease associated with SCD. The issue with ECG screening has been the concern overall for high false positive rates. The low specificity may be related to the choice of ECG criteria to be used; in general, many ECG findings that would be of great concern in elderly adults are completely innocuous when seen in healthy children and young adults. This has led to the development of a variety of ECG screening criteria to help differentiate normal ECG findings in athletes from abnormalities of the ECG that would suggest disease. The European Society of Cardiology criteria, the Seattle criteria, and the Refined criteria have helped to significantly reduce false positive rates related to ECG screening[18, 19]. However, these screening criteria are developed for a specific target population of competitive

and recreational athletes and a specific age range. SCDY occurs in all of the age ranges and does not occur only in athletes.

While data are available related to false positive rates for screening with any of the data elements noted above, the actual population incidence of SCD in the young is unknown. Therefore, the false negative rate (missing an individual who later succumbs to SCDY), is unknown for any combination of screening data elements.

Overall the principal points of consensus on optimal screening methods for SCDY from the Think Tank included: 1) no single test or aspect of history and physical suffice; 2) combined history, physical and ECG is the most fertile approach but there is much to learn about specifically which data elements have most predictive accuracy; 3) smaller more efficient data requirements could support higher quality (completeness, accuracy) screening efforts overall, and that 4) consistency in the use of structured core data elements across screening programs could greatly enhance poolability of data and knowledge accruing from these efforts.

Current State of Screening in the US – Results of a National Survey

To assess the landscape of screening efforts in anticipation of this Think Tank, a thirty-question survey was sent out nationally to public screening organizations. Fifty-five youth screening organizations were identified and contacted. Twenty-eight (51%) responded to the survey. Two of these were omitted from analysis (completed demographics but did not complete survey) and, therefore, twenty-six responses (47%) were included. The survey focused on determining current practices and whether the responding organizations were willing to participate in sharing data in a national repository for future research.

Over 80% of the screening organization respondents currently are private or public foundations while a minority (~15%) are hospital-based or physician-led programs. These organizations are spread across the continental US. Initial screening groups started in the late 1990's while most others began after 2005. A large proportion of the organizations are funded through private donations or other philanthropic support. A smaller proportion have funding through corporate grants or hospital-based support mechanisms. A fraction of these screening groups are for-profit or charge a screening fee. In ~40%, screening is free. A fee is charged (<5%) or a donation is suggested (<25%) in others.

Eighty percent of the respondents screen high school age youths. Primary school age and/or college age youths are screened in 30-40% of the groups. In ~40% of the respondents, youths are screened down to age 5 years and teachers and coaches may also be included. Over 80% of the screening in these groups includes all individuals, regardless of athletic status.

When asked about volume of screening performed, over 25% of the respondents screen over 3000 individuals annually while one-third screen 100-500 youths annually. These rates have resulted in hundreds of thousands of individuals screened in some capacity by these organizations.

Each group was asked about the components of their screening process. Personal and family history are obtained by ~65%. A complete or limited physical exam is performed by approximately half of the groups. The ECG is obtained by over 95% and a 'screening' echocardiogram is performed by 40-50%. Echocardiography used selectively, based on initial screening elements, is performed by just under 40% of the groups. Other elements such as height, weight, and blood pressure are obtained in 60-70%.

There is significant variation regarding other aspects of the screening process itself. Almost 70% of the groups obtain an informed consent or waiver that is signed by both a parent and the child. For groups that give a physical exam as part of their process, there are a range of medical professionals performing this step including primary care physicians, pediatric cardiologists, adult cardiologists, sports medicine physicians, nurse practitioners, and nurses. Regarding 'reading' or interpretation of the ECG, most groups utilize a pediatric or adult cardiologist though a small proportion use a primary care physician, sports medicine physician or nurse practitioner. Regarding follow up after screening, almost 70% of groups report follow up of positive screening via a personal contact via email, phone, or mail. Almost 90% recommend those with a positive screen to follow up with a medical provider.

The survey was used to evaluate data collection methods. Of the 77% who collect history and physical information, approximately 26% store this information in paper form only while another 26% store a combination of paper records and electronic information. A smaller fraction of groups collect and store the data digitally. There is also variation in storage of ECG information. Approximately one third of the groups store ECGs in paper form only. Another 30% use some combination of paper and electronic form and a smaller proportion store ECG data digitally. Of the 73% that perform echocardiography, a larger proportion of the groups store

information on paper only compared to those that use only digital data storage. The respondents were asked about sharing data in the form of a national data repository. Participation was partly dependent upon funding with 50% willing to submit data regardless of funding and just over 40% would only participate if there was funding for the process. The overall results of the survey demonstrate heterogeneity of personnel, screening methods, data collection, and data storage across currently active public screening groups.

Coming Together to Improve Screening Efforts in the US

In the United States today we have a variety of community, non-profit, academic, school-based and for-profit medical groups performing screenings in multiple locations, all with a common goal – to save young lives – but with disparate methods, motivations and ideas how to achieve this goal. This Think Tank successfully enabled dialogue between diverse stakeholders to agree that while cardiac screening efforts are ongoing, there needs to be a synergy of effort with collaboration that allows determination of best practices, impact on public health, and “living/learning” knowledge updates and public reporting to facilitate ongoing improvements. The consensus first step forward was to improve the consistency and quality of data being collected across the diversity of screening programs. The consensus thus focused on promoting efforts to define a minimum mandatory core set of data elements for SCDY screening that could be practically implemented across multiple independent screening groups. Once agreement on a structured minimum core set of consistently acquired data elements is achieved, these data could meaningfully be combined for analysis in ways that are not possible across the current screening landscape. Pooled data that has been collected in a consistent manner allows increased power to identify pivotal elements in the history, physical examination, electrocardiogram, echocardiogram or other technology that indicate either normal variants or key indicators of risk for SCD. As stated in the classic document published by the World Health Organization (WHO) in 1974, pooled data are key to effective collaborations formed to understand and solve complex medical problems[20]. Furthermore, for cardiac screening in the young overall, given the high percentage of normal individuals being screened, pooled data will provide a critical substrate to advance the definition of normal values across the population, with the ability to stratify across key variables such as age, gender, ethnicity, etc. It was well appreciated in Think Tank discussion that the more advanced and articulated the definition of “normal” could reach in

actively developing pediatric populations, the more sensitive and specific comparative definitions of abnormal would become. Thus the Think Tank moved toward a learning health system model objective, e.g. a reliable and sustainable national resource created by the centralized collection of structured, high quality, poolable data obtained across the diversity of the population with public domain access for research and analysis by stakeholders in this effort.

Conclusions and Future Directions

SCDY is a national and international public health problem that requires a multidisciplinary approach to its prevention. The overall issue of screening individuals for diseases that could lead to sudden death is complex. Despite the challenges, screening is ongoing. Given the relative low frequency of sudden death, the variability of efficacy in detection of high-risk cardiac diseases in individuals, and the variability of factors that lead to sudden death in those individuals, the most pragmatic approach to improvement of screening efficacy and potential protection of high-risk individuals from sudden death is to develop consensus agreement on screening methods, including definition of a structured core minimum set of data elements that can be pooled across individual screening efforts and made available in the public domain to interested stakeholders. In addition to these first steps, discussions also emerged around challenges such as the mechanisms and resources for collection and storage of long term follow up information about screened individuals, development of a centralized data registry, and continuous data analysis with resultant iterative process improvement. The path to success depends upon active collaboration that utilizes the ongoing and extensive work being done already by screening groups, but in a manner that leads to a high quality national resource that can continue to learn as knowledge accrues. The establishment of this resource will enable defining normal values, stratified across the diverse population, enable improvements of methodology and technology to detect abnormalities that put children at risk of sudden death, and potentially enhance predictive capability of SCDY risk related to drug exposure.

As a result of this Think Tank, a core leadership working group has been assembled and will meet regularly with a mission to develop a national screening resource as discussed above. The success of this mission is dependent on broad representation to reach consensus. Therefore,

this effort will proceed under the structure of the CSRC and its guiding principles of broad inclusion of stakeholders across academic, public, industrial, and regulatory sectors.

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ACCEPTED MANUSCRIPT

Appendix A: Screening Groups

Anthony Bates Foundation

Nicholas Ryan Over Foundation

Nick of Time Foundation

Parent Heart Watch

R. Andrew Helgeson Memorial Foundation

Simon's Fund

Who We Play For

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