Notes of the UK National Screening Committee Stakeholder Meeting On Screening for Sudden Cardiac Death in Young People

9th December 2009

Rooms 3&4, 50 Eastbourne Terrace, LONDON

Attendees:

Dr Anne Mackie, Programme Director UK National Screening Committee (Chair)
Dr James Barry, Cardiologist, Wales
Dr Elijah Behr, Cardiologist, England
Dr Margaret Boyle, DH, Social Services and Public Safety, NI & member of UK NSC
Dr Frank Casey, Paediatric Cardiologist, Northern Ireland
Dr Campbell Cowan, Cardiologist, England
Steve Cox, Cardiac Risk in the Young
Sarah Cromwell, Screening and Specialised Services Team, Dept of Health, England
Dr Iain Findlay, Cardiologist, Scotland
Dr Nick Hicks, Health Technology Assessment
Professor Stuart Hillis, Cardiologist, Scotland
Dr Pascal McKeown, Cardiologist, Northern Ireland
Will Scott, Scottish Government
Shiraz Sethna, Vascular Programme, Department of Health England
Professor Sanjay Sharma, Cardiologist, Cardiac Risk in the Young
Dr Ros Skinner, Scottish Government and member of the UK NSC
Dr Graham Stuart, Arrhythmia Alliance
Professor Peter Weissberg, Cardiologist, British Heart Foundation
Dr Christopher Wren, Paediatric Cardiologist, England

Speakers:

Professor Ken Stein, Peninsula Medical School
Dr Julian Elston, Peninsula Medical School

Report Writers:

Dr Rosalind Griffiths, SpR Public Health Wales
Dr Alan Rankin, SpR Sports & Exercise Medicine Northern Ireland

1 Welcome and Introductions:

The stakeholder meeting on screening for sudden cardiac death was chaired by Dr Anne Mackie, Director of Programmes, UK National Screening Committee (UK NSC).

Following a formal welcome of attendees and introductions the aim of the meeting was stated. The purpose of the meeting was to explore if there are specific questions on screening for sudden cardiac death (SCD) which can be answered by further research in this area.

The background to the meeting was that the UK NSC had commissioned an update review of the evidence on a population screening programme for hypertrophic cardiomyopathy (HCM) that was completed in late 2008. In November 2008, the UK NSC accepted the review which concluded that screening should not be offered and that pre-participation screening of athletes for HCM or other causes of SCD should not be instituted at present. It also recommended that consideration should be given to commissioning further research into the value of screening competitive athletes for SCD.

This meeting set out to discuss the evidence submitted in the review in order to establish future areas and priorities in research on population based screening for SCD. The facilitated discussion would be used to develop genuine research questions and the future means of taking this research forward. This was not designed to be a forum in which to debate the arguments for and against population based screening for SCD.

2 Evidence Review for Screening for the Risk of Sudden Cardiac Death:

Professor Ken Stein presented a review of the literature examining the role of screening for the risk of SCD. This was based on the review commissioned by the UK NSC on population screening for HCM prepared by Ken Stein and Julian Elston in July 2008. In July 2008, the UK NSC discussed the report and gave comments on the report to Julian Elston. The report was finalised for the November 2008 meeting of the UK NSC and the policy statement on HCM was agreed by members at this meeting.

The presentation covered definitions of SCD, size of the problem, aetiology, screening tests, effectiveness of treatment and screening programmes, cost effectiveness and uncertainties. (Copy of presentation at Annex 1).

The term ‘Sudden Cardiac Death,’ has varying definitions within the academic literature and as such has created some difficulties with the interpretation and comparison of data between sources. In the UK at present there is no official register of these events and thus incidence rates depend on the accuracy of pathology, registrar general and hospital record data.[post meeting note. The DH reported that there is a register “The sudden Cardiac Death database which is part of the Central Cardiac Audit Database (CCAD). It was launched in Nov 2008 and has been funded by DH from the outset. UK Cardiac

Pathology Network pathologists enter data onto the database which was very recently updated.]

Owing to the multiple causes of SCD and the ambiguity of data collection, the accurate estimation of the incidence of death from these conditions is extremely difficult and unreliable. Estimates from specialised registers established in Sweden, Italy and the USA are useful in providing this baseline information.

The causes of SCD are multiple and varied including myocardial ischaemia, cardiomyopathies, infective causes and connective tissue conditions. The majority of cases of SCD in the general population are due to ischaemic heart disease which predominates in later life. In the under-35 age group HCM predominates in the USA, while arrthymogenic right ventricular cardiomyopathy (ARVC) causes the majority of deaths in this population in Italy. Exercise itself has been identified as a risk factor for SCD in several studies with a higher relative risk of SCD in athletes versus non-athletes. The absolute risk for these events in both groups remains very low.

In the literature three methods of screening are currently used to identify those at risk of SCD. These are 12-lead electrocardiogram (ECG), medical history (personal and family) and physical examination. The current approach in the USA is to use history and examination only, while the Italian National Athlete Screening Program uses the ECG in addition to these. Varying estimations exist regarding the sensitivity and specificity of combinations of the three screening tests with American studies suggesting that there is little increased benefit in the addition of the ECG in contrast to Italian data which supports this stance favourably. Some significant causes of SCD cannot be identified even with the addition of ECG including; coronary artery disease, coronary artery anomalies, ARVC and long-QT syndrome with incomplete penetrance. Physical conditioning can lead to ECG abnormalities which are physiological. These may be identified as pathological by the inexperienced interpreter and lead to false positives.

When an individual is identified through screening, they often require further investigation to diagnose any underlying pathology. These tests include echocardiography, genetic tests and cardiac magnetic resonance imaging. The evidence of the performance of diagnostic tests in those individuals identified as positive during screening is limited. Once a disease or condition has been identified, treatment proposed will vary according to the underlying condition, risk of life threatening arrhythmias and the technical performance of treatment. Various treatments exist including exercise avoidance, surgery, ablation, medication and implantable cardiac defibrillators. Trials evaluating the necessity and effectiveness of the majority of these treatments are lacking and prognosis and optimal management for differing severities of individual conditions is yet to be firmly established.

The majority of the evidence on the effectiveness of screening for SCD in the prevention of premature mortality comes from Italy where annual screening of athletes has been carried out since 1982. Italian studies looking at mortality rates in the Veneto region have demonstrated a reduction in mortality rates in screened athletes over a period of 20 years to below that of the general population. This data is however open to interpretation, as other possible confounding factors occurring over the last 20 years were not taken into account. According to the presenters, the data, when examined for reduction in mortality rate due to HCM alone, demonstrated no statistically significant difference. False positive rates of 7-8% were seen and 2.1% of athletes were disqualified from participation in sport. Figures have been quoted for the cost-effectiveness of the Italian model of screening involving ECG compared to the American model. Italian data, while conforming favourably compared to the estimates of the American costing model, has gaps in the estimates leading to potentially flawed cost-effectiveness studies.

Assessing the value of screening is difficult and performing high quality randomised controlled trials is extremely difficult, if not impossible, due to the large numbers and length of follow-up that would be required. Other factors influencing screening include level of uptake, cost of implementation and the social, financial and psychological impact of a failed test whether truly or falsely positive and unfortunately there will still be adverse events.

Many areas of uncertainty and questions remain around screening for SCD.

Population:

- What population should be considered for screening?
- What are the underlying causes of SCD in the UK in the target population? What is their prevalence and incidence?
- What is the prognosis, in terms of SCD, for each of the disorders of interest?

Test performance:

- What is the diagnostic performance of screening tests for each of the disorders?
- What is the diagnostic performance of confirmatory tests in screen positive cases?

Interventions:

- What is the effectiveness of treatments to prevent SCD in the target population with the disorders of interest?

Harms and attitudes:

- What are attitudes to screening amongst the target population?
- What is the understanding of potential harms?

Cost and cost effectiveness:

- What are the cost effectiveness and budget impact of screening?

Future research should be directed at answering some of the issues that are detailed in order to fill the deficits that exist within the current evidence base.

3 Discussion:

Anne Mackie clarified that the purpose of the discussion was not to decide on whether to screen for SCD but to discuss about possible areas of research that could be pursued.

Peter Weissberg stated that the priority is to identify families and first degree relatives of people who had SCD. Graham Stuart asked that it should to be clarified whether it was only athletes that were being discussed and also the definition of an athlete. Stuart Hillis said that raising the profile of risk related to exercise would be counterproductive to the messages related to the positive health benefits of exercise. He noted that mandatory screening takes place at the highest level of sport as directed by FIFA and the IOC.

Anne Mackie stated that the UK National Screening Committee is set up for screening for conditions and not a 'risk'. The issue here was not about screening for one condition but a set of conditions and if research could be pursued, a few specific conditions at a specific age, rather than all conditions, should be identified for further research. Steve Cox suggested that it would be problematic to screen for only one or two conditions as other conditions or abnormalities would be identified on ECG for example. Ken Stein said that in the case of ECG, a defined set of conditions could be identified and the same applies to physical examination.

It was noted that the incidence and lifetime risk of SCD is not known and that rates quoted in the UK differed. Iain Findlay stated that most data is from high risk tertiary referral centres but the risk related to a typical 17 year old who presents with an abnormal ECG is unknown. A true risk of the outcome of these abnormalities is needed.

Sanjay Sharma said that the presentation reinforced the negative aspect of screening but that the Italian data is post-mortem data and therefore hard evidence. Jonathan Drezner's studies on athletes in the USA reported an incidence of 1 in 25,000 which was the same as the Italian data.

As Ken Stein stated in his presentation, the population at risk has not been defined. This was discussed by the attendees and agreed that it would be important to define. Elijah Behr said that in younger people genetic disease is more important and some conditions such as ARVC have an age related penetrance. The age range of the population to screen and the frequency of screening should be decided and the need for pilot studies was suggested. Anne Mackie stated that pilot studies would imply that there is an intention to screen but this has not been confirmed. She suggested that input regarding funding for research would be more appropriate. Peter Weissberg said that the Medical Research Council (MRC) would not be interested in funding this

type of research because it is unlikely that research would be able to provide the answers to the questions raised today.

The need for a National Register was raised. Stuart Hillis suggested a register of events of SCD in athletes divided into age groups. He mentioned that in Scotland all deaths under the age of 45 years had been analysed and most deaths that occurred on sports grounds were violent deaths unrelated to SCD.

Shiraz Sethna described the SCD database. This database is part of the Central Cardiac Audit Database (CCAD). It was launched in Nov 2008 and has been funded by DH. UK Cardiac Pathology Network pathologists enter data onto the database.

Will Scott reported that pathologists in Scotland were also feeding into this database. Northern Ireland also contributes to it. There were concerns that as this database was dependent on pathologists reporting cases there was likely to be under-reporting. Questions were raised about the quality of pathology in SCD, the difficulties in maintaining the SCD register and so whether it was fit for purpose. Office for National Statistics (ONS) statistics and Coroner's statistics were not helpful due to poor reporting. Elijah Behr described a database that Heart Rhythm UK are considering which is to keep a database of people as they present, with a genetic abnormality or abnormal electrophysiology with phenotype, and to follow them up over a 5 year period. This would be an attempt to identify the prevalence of conditions and the natural history in the UK, which may help to give a more accurate prognosis. They are seeking BHF funding for this database.

Stuart Hillis noted that there was fully funded genetic testing in Scotland for families of individuals who had SCD and the pick-up rate of genetic abnormalities was 90% for some conditions. Professor Weissberg said that the BHF, in conjunction with the Department of Health, offer a Genetics Advice Service to relatives of a sudden death victim that provides them with Information on SCD and a letter to their GP prompting referral to the nearest Inherited Cardiac Conditions centre for assessment and genetic testing if appropriate. It is intended that coroners should alert families of SCD victims to this service, but this rarely happens.

Graham Stuart said that ideally a longitudinal study of untreated people should take place as the natural history without intervention is unknown. SCD can be under diagnosed. There is often a history of a death of a young person in the family such as a motorcycle death or a swimming death. They may have had SCD but the death would have been registered as accidental death or drowning.

The risk of SCD was discussed and Julian Elson stated that the best available data shows that the incidence is 1/100,000 person-years. Ken Stein said that we could never be sure what the risk is and the small numbers from the Italian study meant that it was difficult to make predictions about populations. Sanjay Sharma acknowledged that it was very difficult to identify individuals' risk of

SCD but the Italian study gives us some data i.e. athletes who had HCM compared with no HCM had a relative risk of 3 of sudden death. Julian Elson raised the point that the 55 deaths in the Italian study would not all have been prevented by screening; such is the nature of screening programmes.

Pascal McKeown raised the issue of natural history of abnormal ECGs with no associated genetic or morphological abnormality, and said that currently the appropriate management of these people is unknown. They are followed up with an unknown prognosis. The natural history of these also needs to be identified.

Discussions about the Italian data included questions about why only data from the Veneto region in Italy was available when the screening programme includes the whole of Italy. In addition, the definition of athlete was thought to be poor, and some data was coming from the general population.

Ros Skinner said that these questions would remain unanswered without the right information for example, about genotype. She suggested that it would be feasible to set up an active surveillance database as there were only a small number of genetic laboratories. It should also involve pathology, coroners, genetics, laboratory and clinical staff and would be similar to the CJD database based in the Surveillance Unit, Edinburgh which had contributions by neurologists, pathologists and geneticists. The point was raised that unlike SCD, CJD has a defined phenotype. This surveillance system would need a lot of money and widespread participation. Other attendees thought that the phenotype of SCD could be defined and that there would be enough interested physicians to take part.

Margaret Boyle asked whether some of this information could be obtained by looking at currently available data, such as data from the Whitehall studies. Elijah Behr commented that not all of the study participants had ECGs and are mostly middle aged men. Julian Elston mentioned a prospective study that is underway in the Netherlands. He said that there were over 400 genetic variations for HCM which would make accurate and comprehensive genetic screening of all abnormalities almost impossible.

Frank Casey said that a better understanding was possible through the follow up of immediate family members of people who had SCD as they were more likely to have a positive result. He added that in Northern Ireland, families are often advised by the coroner to attend their GP for screening to be organised. Peter Weissberg said that the BHF had identified 16 families but they had not been referred via the coroner. Steve Cox said that some families had faced difficulties in obtaining a referral to a Cardiologist via the GP. He suggested looking at CRY data.

Christopher Wren said that there was no data on children and no information about the risk of SCD, and no evidence that ECGs can find these abnormalities in children. Those with Long QT syndrome usually have symptoms before 14 years of age and a number will have died, so by looking at adults the wrong age group are being studied. He said that family history is

of no use for new mutations. Steve Cox said that CRY did begin screening children under 14 years in Northern Ireland but they had to stop as too many were being recommended for repeat screening. This was also causing a lot of distress to the families. Sanjay Sharma said that there are many additional, difficult to interpret ECG abnormalities in children, so CRY screen from the age of 14 years. The point was made by an attendee that when people go to CRY to be screened they perceive that they have been screened comprehensively for SCD.

The topic of screening neonates for sudden infant death syndrome (SIDS) was raised but this was thought to be extremely unlikely.

Methods of gathering information were discussed; these included identifying from coroners, people who may have had SCD and following up their families, and surveillance of cases by experts in the field using a properly organised network. Identifying people at risk through laboratory genetic services or people with abnormal ECGs and following them up was also thought to be a viable option. The general consensus was that a register would be beneficial. It was felt that finding out more about the natural history of people with abnormalities is aligned with recommendations from Chapter 8 of the Coronary Heart Disease National Service Framework.(I am not quite sure what this means) Anne Mackie stated that the UK National Screening Committee would not be in a position to host the register and this would have to be done by a research organisation. She suggested that any research may not be possible as a UK wide exercise. It was agreed that the number of ethics committees that would have to be approached could be a barrier to UK wide research, although due to the relatively small number of sudden cardiac deaths it would be advantageous to involve as many people as possible. Though this was not a major issue with MREC approval. Ros Skinner suggested discussing the genetic issues with the UK Genetic Network Testing Steering Group.

Nick Hicks said that the HTA programme fund RCTs or evidence synthesis so HTA could be involved further downstream. The questions that need answering are not questions that could be answered by the HTA but evidence synthesis or modelling could be done.

It was agreed that an RCT would not be possible. The British Heart Foundation would consider applications to help fund initial research or pump prime the establishment of a register but would not be able to make a long term commitment.

Campbell Cowan indicated that there is some interaction between genotype and exercise citing the new presentation of ARVC in endurance athletes. Sanjay Sharma is currently reviewing a paper on endurance athletes and ARVC. Peter Weissberg said that as much phenotypic data as possible would be needed in the database as in a few years there would be a lot of information on genotype.

Margaret Boyle suggested that the Millennium Cohort Study would be an opportunity to collect data, assuming they would all have an ECG but Anne Mackie asked what would be done with the answers. Graham Stuart said that the ECGs would be for longitudinal follow up only. The UK Biobank was suggested as a means for obtaining ECGs but it was noted that this only included people who were over the age of 35 years. Anne Mackie suggested that these issues be discussed in a Cardiology forum. She added that there was huge political interest from all 4 countries and that it was a reasonable proposal to look at some of these issues with an expectation of getting some financial input. Sanjay Sharma added that CRY intended to offer Italian model screening to all children born in 1995 in the South East of England and to follow them up for 5 years. They are currently seeking ethical approval.

4 Summary points:

Anne Mackie summarised the discussion saying that there appeared to be consensus on three areas where further work should be considered:

1) The prevalence of SCD needs to be established.
2) More information is needed on the natural history of people found to have a problem.
3) Improving the care and follow-up of close relatives of victims of SCD in line with recommendations in Chapter 8 of the CHD National Service Framework.

5 Action points:

The following action points were agreed and members were asked to take them forward.

- Ros Skinner to pursue, with the UK Genetic Testing Network Steering Group, access to information on outcome of genetic testing and establishing their co-operation and participation in a national register.
- Elijah Behr to pursue with Heart Rhythm UK the setting up of a register/database of people with a genetic abnormality or abnormal electrophysiology with phenotype. The aim of it would be to follow up patients, gather clinical and genetic information and review cases and family members.
- CRY offered to make available what they had on those they had screened/gather additional information in their screening protocols in order to assist in provision of data for future research.