REPORT ON MEDICAL DEVICE ROUNDTABLE

Adopting Best Practices for Post-Market Surveillance of Medical Devices in Singapore

Grand Copthorne Waterfront Hotel

Friday 15 March 2013

Chair: Professor Ranga R Krishnan, MB ChB
Dean and Professor
Duke-NUS Graduate Medical School, Singapore

Co-chair: Professor Mitchell W Krucoff, MD
Director, Cardiovascular Devices Unit, Duke Clinical Research Institute, US
Special Government Employee, U.S. Food and Drug Administration

® Health Sciences Authority, Singapore
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# Abbreviations

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<th>Abbreviation</th>
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<tbody>
<tr>
<td>ACC</td>
<td>American College of Cardiology</td>
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<td>AOA</td>
<td>Australian Orthopaedic Association</td>
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<td>ARC</td>
<td>Academic Research Consortium</td>
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<td>ASPECT</td>
<td>Asia Pacific Evaluation of Cardiovascular Therapies Collaboration</td>
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<td>BHR</td>
<td>Birmingham Hip Resurfacing</td>
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<td>BMI</td>
<td>Body Mass Index</td>
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<td>BOA</td>
<td>British Orthopaedic Association</td>
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<td>CDRH</td>
<td>Center for Devices and Radiological Health</td>
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<td>CE</td>
<td>Communauté Européenne</td>
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<td>CMS</td>
<td>Centers for Medicare and Medicaid Services</td>
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<td>CRF</td>
<td>case report form</td>
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<td>CRO</td>
<td>contract research organisation</td>
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<td>CRT</td>
<td>Cardiac Resynchronisation Therapy</td>
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<td>DAPT</td>
<td>Dual Antiplatelet Therapy</td>
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<td>DELTA</td>
<td>Data Extraction and Longitudinal Time Analysis System</td>
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<td>EDC</td>
<td>electronic data capture</td>
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<td>EHR</td>
<td>electronic health record</td>
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<td>EMEA</td>
<td>European Medicines Agency</td>
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<td>EMR</td>
<td>electronic medical report</td>
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<td>GHTF</td>
<td>Global Harmonization Task Force</td>
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<td>HSA</td>
<td>Health Sciences Authority</td>
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<td>HTA</td>
<td>Health Technology Assessment</td>
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<tr>
<td>ICD</td>
<td>implantable cardiac defibrillator</td>
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<td>ICOR</td>
<td>International Consortium of Orthopaedic Registries</td>
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<td>IDE</td>
<td>Investigational Device Exemption</td>
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<td>IMACS</td>
<td>International Mechanically Assisted Circulatory Support</td>
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<td>INTERMACS</td>
<td>Interagency Registry for Mechanically Assisted Circulatory Support</td>
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<td>J-MACS</td>
<td>Japanese Registry for Mechanically Assisted Circulatory Support Model</td>
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<td>MDEpiNet</td>
<td>Medical Device Epidemiology Network Initiative</td>
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<td>MedSun</td>
<td>Medical Product Safety Network</td>
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<td>MHLW</td>
<td>Japanese Ministry of Health, Labour and Welfare</td>
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<td>MHRA</td>
<td>Medicines and Healthcare Products Regulatory Agency</td>
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<td>NCDR</td>
<td>National Cardiovascular Data Registry</td>
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<td>NHS</td>
<td>National Health Service</td>
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<td>NIH</td>
<td>National Institutes of Health</td>
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<td>Abbreviation</td>
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<tr>
<td>NJR</td>
<td>National Joint Registry</td>
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<td>NJRR</td>
<td>National Joint Replacement Registry</td>
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<td>NRIC</td>
<td>National Registration Identity Card</td>
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<td>OEWG</td>
<td>Orthopaedic Expert Working Group</td>
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<tr>
<td>PCI</td>
<td>percutaneous coronary intervention</td>
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<td>PMDA</td>
<td>Pharmaceuticals and Medical Devices Agency</td>
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<td>RFID</td>
<td>radio frequency identification</td>
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<tr>
<td>SCAAR</td>
<td>Swedish Coronary Angiography and Angioplasty Registry</td>
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<td>SCDB</td>
<td>Singapore Cardiac Data Bank</td>
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<td>SGH</td>
<td>Singapore General Hospital</td>
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<td>SME</td>
<td>Small and Medium-sized Enterprises</td>
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<td>TAVR</td>
<td>Transcatheter Aortic Valve Replacement</td>
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<td>TGA</td>
<td>Therapeutic Goods Administration</td>
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<tr>
<td>TVT</td>
<td>Transcatheter Valvular Therapy</td>
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<tr>
<td>UDI</td>
<td>Unique Device Identification</td>
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<tr>
<td>U. S. FDA</td>
<td>United States Food and Drug Administration</td>
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<td>VAD</td>
<td>Ventricular Assist Devices</td>
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Speakers and panellists

Opening remarks

- **Dr Amy Khor**, Minister of State, Ministry of Health and Ministry of Manpower, Singapore *(Guest of Honour)*
- **Associate Professor John Lim**, Chief Executive Officer, Health Sciences Authority, Singapore
- **Professor Ranga R Krishnan**, Dean, Duke-NUS Graduate Medical School, Singapore
- **Professor Mitchell W Krucoff**, Director, Cardiovascular Devices Unit, Duke Clinical Research Institute, USA
- **Mr John Wilkinson**, Director of Medical Devices, Medicines and Healthcare products Regulatory Agency, UK
- **Dr Thomas Gross**, Director, Office of Surveillance and Biometrics, Center for Devices and Radiological Health, United States Food and Drug Administration, USA

Session 1: Device registry – Orthopaedic

- **Professor Stephen Graves**, Chair, Australian Joint Registry and International Consortium of Orthopaedic Registries, Australia
- **Dr Jane Cook**, Head, Office of Product Review, Therapeutic Goods Administration, Australia
- **Dr Aran Maree**, Chief Medical Officer, Medical Devices and Diagnostics, Johnson & Johnson
- **Associate Professor Inderjeet Singh Rikhraj**, Chairman, Chapter of Orthopaedic Surgeons, Singapore General Hospital, Singapore
- **Professor Ranga R Krishnan**, Dean, Duke-NUS Graduate Medical School, Singapore
- **Associate Professor Low Cheng Ooi**, Chief Medical Information Officer, Ministry of Health, Singapore
- **Dr Stuart Portnoy**, Senior Consultant, Medical Devices, Biologics Consulting Group, USA
- **Professor Tay Boon Keng**, Clinical Professor, Department of Orthopaedic Surgery, Singapore General Hospital, Singapore
- **Mr John Wilkinson**, Director of Medical Devices, Medicines and Healthcare products Regulatory Agency, UK
Session 2: Device registry – Cardiovascular

- **Dr Madoka Murakami**, Unit Chief, Division of Regulatory Cooperation, Office of International Programs, Pharmaceuticals and Medical Devices Agency (PMDA), Japan
- **Professor Ralph Brindis**, Past President, American College of Cardiology, US
- **Ms Roseann White**, Director, Global Biometrics, Abbott Vascular
- **Associate Professor Lim Soo Teik**, Head, Department of Cardiology; Director, Cardiac Catheterization Laboratory, National Heart Centre Singapore. Chairman, Chapter of Cardiologists, College of Physicians, Academy of Medicine Singapore
- **Professor Mitchell W Krucoff**, Director, Cardiovascular Devices Unit, Duke Clinical Research Institute, USA
- **Associate Professor Lim Chong Hee**, Director and Senior Consultant, Heart and Lung Transplant Programme Department of Cardiothoracic Surgery, National Heart Centre, Singapore
- **Mr Michael Gropp**, Vice President, Global Regulatory Strategy, Medtronic Inc., USA
- **Mr Kazuo Kawahara**, Manager, Clinical and Regulatory Affairs, Terumo Corporation, Japan
- **Dr Stuart Portnoy**, Senior Consultant, Medical Devices, Biologics Consulting Group, USA
- **Mr Daniel Verstappen**, Vice President, Quality and Regulatory Affairs, GE Europe Healthcare
- **Mr Rainer Voelksen**, Vice President, International Regulatory Affairs, Edwards Lifesciences, Paris, France

Session 3: Roundtable discussion on establishing device registries

- **Professor Ranga R Krishnan**, Dean, Duke-NUS Graduate Medical School, Singapore
- **Professor Mitchell W Krucoff**, Director, Cardiovascular Devices Unit, Duke Clinical Research Institute, USA
- **Professor Aung Tin**, Head and Senior Consultant, Glaucoma Service, Singapore National Eye Centre, Singapore
- **Professor Ralph Brindis**, Past President, American College of Cardiology, USA
• **Associate Professor Chan Cheng Leng**, Deputy Group Director, Health Products Regulation Group, Health Sciences Authority, Singapore

• **Dr Jane Cook**, Head, Office of Product Review, Therapeutic Goods Administration, Australia

• **Professor Stephen Graves**, Chair, Australian Joint Registry and International Consortium of Orthopaedic Registries, Australia

• **Mr Michael Gropp**, Vice President, Global Regulatory Strategy, Medtronic Inc., USA

• **Mr Kazuo Kawahara**, Manager, Clinical and Regulatory Affairs, Terumo Corporation, Japan

• **Associate Professor Koh Tian Hai**, Medical Director, Medical Director’s Office, National Heart Centre, Singapore

• **Associate Professor Lee Chien Earn**, Chief Executive Officer, Changi General Hospital, Singapore

• **Associate Professor Lim Soo Teik**, Head and Director, Department of Cardiology, Cardiac Catheterisation Laboratory, National Heart Centre, Singapore

• **Associate Professor Low Cheng Ooi**, Chief Medical Information Officer, Ministry of Health, Singapore

• **Dr Aran Maree**, Chief Medical Officer, Johnson & Johnson, Medical Devices and Diagnostics

• **Dr Madoka Murakami**, Unit Chief, Division of Regulatory Cooperation, Office of International Programs, PMDA, Japan

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• **Ms Roseann White**, Director, Global Biometrics, Abbott Vascular

• **Mr John Wilkinson**, Director of Medical Devices, Medicines and Healthcare products Regulatory Agency, UK

• **Associate Professor Yeo Seng Jin**, Senior Consultant, Department of Orthopaedic Surgery, Singapore General Hospital, Singapore
Executive summary

Medical device registries serve as one of the emerging essential tools in safeguarding public health. High-risk implantable medical devices can be associated with adverse events that may occur years post-operatively, so the ability to monitor and trace patients and the manufacturer of their device is vital when a serious safety issue is detected. Registries enable large bodies of diverse data about a device to be collected. Registries implicitly implement the use of consistent endpoint definitions, which further facilitate the detection of signals about device safety in the real world. They can be used to determine the nature and frequency of reported adverse events for ‘track and trace’ purposes, and in the longer term, support clinical outcomes and best practices. Registries have also been shown to provide unique efficiencies for prospective studies, and the “registry based randomized trial” in Sweden and USA had created a new paradigm for “total product life cycle” device evaluations. Finally, clinicians, regulators, academics and device manufacturers all have a vested interest in timely access to registry data, especially early safety signals, so that prompt action can be taken with regard to faulty devices.

In Singapore, data on implanted medical devices are typically kept by individual institutions, but these are generally not centralised even within a single institution. The Health Sciences Authority (HSA) of Singapore has identified the development and implementation of medical device registries as a key post-market surveillance strategy within its regulatory activities aimed at protecting the public. In many countries, medical device registries are used as post-market surveillance tools, mainly for cardiovascular and orthopaedic devices. It is therefore in the interest of public safety to bring together those in Singapore who have a collaborative interest in the data that a registry could provide. The initiative to start medical device registries locally involves many stakeholders and requires a multi-disciplinary team including the MOH, MOHH, hospitals, clinicians, academia, industry and HSA.

To this end, a medical device roundtable was held in Singapore on 15 March 2013. The meeting’s objectives were to:

- create a discussion platform for healthcare professionals, academics, industry stakeholders and regulators, to identify and build on existing international best practices in medical device registry and post-market surveillance
- discuss the practical applications of such registries, with the goal of setting up high-risk device registries, starting with cardiac and orthopaedic registries in Singapore
• examine the processes required to support the implementation and governance of these medical device registries locally as well as their potential for integration as an international health care resource.

Perspectives and recommendations were sought from global regulatory, industry, academic and clinical representatives. Speakers included regulatory experts from some of the HSA’s key partner agencies: the United States Food and Drug Administration (US FDA), the United Kingdom’s Medicines and Healthcare products Regulatory Agency (MHRA), the Australian Therapeutic Goods Administration (TGA), and the Japanese Pharmaceuticals and Medical Devices Agency (PMDA). Distinguished clinical experts hailed from overseas and national institutions that included the American College of Cardiology (ACC) and Duke Clinical Research Institute in the US, the Australian Orthopaedic Association’s National Joint Replacement Registry (AOA NJRR), the International Consortium of Orthopaedic Registries (ICOR), as well as the Singapore National Heart Centre, Singapore National Eye Centre, Singapore General Hospital (SGH) and Duke-NUS Graduate Medical School of Singapore locally.

This report comprises summaries of the presentations and discussions that took place at the roundtable meeting, and the key themes and recommendations that emerged around the development and implementation of cardiac and orthopaedic registries. Introductory presentations provided an overview of existing medical device registries in the US and UK, with a focus on their functions, infrastructure, governance and post-market surveillance outcomes.

**Orthopaedic device registries**

The AOA NJRR and the output it generates provide examples of how a successful orthopaedic registry led to implementing best practices and improving outcomes for patients. SGH’s orthopaedic registry is a hospital-based registry that collects data on patient demographics, type of surgery, peri-operative outcomes, and patient-reported outcomes. Data from this registry have been used to generate numerous publications covering all aspects of orthopaedic surgery.
The medical device industry views itself as an active collaborative partner with regulators in registries for post-market surveillance and risk management. To improve collaboration amongst stakeholders, four key areas of focus were recommended:

1) harmonisation of key definitions
2) implementation of minimum datasets
3) improved statistical tools
4) consistency in global reporting of registry signals

In setting up a new orthopaedic device registry, Singapore could join a well-established international community of registries that will share infrastructure and solutions to challenges. Comparable information across international jurisdictions has unique and informative applicability to signal detection methodologies both specifically in Singapore and globally. Most, if not all registries around the world have been initiated, controlled and owned by clinicians. Therefore, a multi-stakeholder participation will be imperative to establish a medical device registry in Singapore.

Cardiovascular device registries

The design, functions and management of the Japanese Registry for Mechanically Assisted Circulatory Support Model (J-MACS), were described. Also described were the stakeholders, benefits and outputs of the National Cardiovascular Data Registry (NCDR’s) eight US-based registries. To maintain their long-term sustainability and viability, the attending experts recommended that registries should be tailored to fit more efficiently into the post-market surveillance environment. Automated surveillance can fill gaps in current passive reporting approaches by monitoring accruing datasets for low frequency safety signals, using pooled registry data from several high-volume centres globally.

Medical device manufacturers are strongly in favour of cardiovascular device registries because they facilitate post-market surveillance that enables them to improve device efficacy and safety. Collaboration between regulators, academia and industry is vital to the development of registries that are informative and that both identifies and potentially provides efficient solutions for addressing currently unmet needs. Processes for escalating and acting on potential safety signals must also be established.
The aim of the Singapore Cardiac Data Bank (SCDB) is to maintain a registry of cardiovascular diseases and relevant procedures performed in Singapore. Providing the comprehensive patient data required by the SCDB is currently perceived as burdensome by Singapore’s clinicians. It will therefore be important, when establishing a national cardiovascular-related device registry in Singapore, to ensure that simple and complete data accrual processes can be fluidly integrated into clinical work flow, for example by linking the registry to electronic medical reporting. Furthermore, local residents have National Registration Identity Card (NRIC) numbers, and Medisave claims can be linked to the implants used in individual patients – these factors should in theory facilitate device tracking and signal detection. In the future, it is also possible that international standards for unique device identifiers (UDIs) will further enhance track and trace capabilities without increasing work burden.

Because Singapore has a relatively small population, a national cardiac device registry may be underpowered to detect rare catastrophic events. International collaboration or data pooling would increase the certainty of rare signal detection, although challenges such as database linkages, information extraction and data security would need to be addressed. The spirit of collaborative objectives and enterprise would also be needed to overcome the intrinsic resistance to data sharing across stakeholders.

Practical suggestions for establishing Singapore’s national cardiovascular device registry included:

- In-depth studies of other registries, such as the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS), to determine the most useful common data fields to be included that will also facilitate data pooling, before adding additional data fields relevant to the Singapore context.

- Merging clinical data obtained at the time of implantation with patient identifiers and hospital administrative data – a process already practised in the US.

- Strategies to encourage clinicians’ participation, which include government mandate, peer pressure to demonstrate centres of excellence, linking participation to reimbursement, and reassurance that registries provide enormous benefits and should not be viewed as punitive tools.
• Strategies to maximize the impact of early efforts, such as enlisting a smaller number of higher volume sites in a “pilot” phase that would nonetheless capture >80% of related procedures performed in the Singapore community

• Potential to model data fields on currently existing registries such as the NCDR

**Next steps**

The final session of the meeting took the form of a plenary roundtable discussion on the next steps and processes needed to establish national medical device registries in Singapore. This was followed by a final call to action for the HSA.

1. The first step will be to achieve consensus on the goals and objectives of each registry, to facilitate its optimal design.
   - The HSA should examine existing options and on-going initiatives in Singapore that can be leveraged for these registries, to prevent duplication of effort and to identify which resources are still required.
   - In addition to HSA and clinicians, other stakeholders should be identified to embark on these initiatives.

2. Given the importance of the role of clinicians in designing and driving registries, positive awareness campaigns should be rolled out to educate physicians and patients about the benefits of national registries as a genuine “national treasure” for health care, and to facilitate their buy-in (for example, articulating the benefit to various stakeholders, such as reimbursements for patients).

3. Steerimg and scientific committees should then be formed to bring these different stakeholders together. Their task will be to determine:
   - consensus mission statements
   - registry goals
   - governance frameworks
   - how to leverage existing international registry designs to establish registries in Singapore
   - protocols to link data or safety signals with action and stakeholder responsibility
   - sustainable financial models.

The examination of structure and governance of existing registries outside Singapore may provide useful “lessons learned” to facilitate organization and progress without creating cumbersome bureaucracy.
4. A primary task will be to expand and convert Singapore’s existing data that are needed for track and trace purposes (i.e. patient identifiers, device identifiers, outcomes and readmission rates) into an electronic format that is consistent and potentially accessible to other registries or databases. The Federated Data System in the US enables data pooling in an anonymous manner using standardised software, and a similar system may encourage the sharing of registry data within Singapore.

Ultimately, the ideal registry monitoring system would have a governance structure based on the roles and responsibilities of all who use the registry, with the establishment of an analytical centre for data mining, information output and reports. In planning such systems, account must be taken of continuous updates on options for new statistical analytical methods, accessibility, alert notifications and feedback to source sites.

In conclusion, this roundtable meeting provided the HSA with the recommendations it needed (described in the next section) to facilitate a collaborative effort with local and global stakeholders to execute registry implementation that can not only achieve medical device traceability in Singapore, but will also improve health outcomes for patients, nationally and globally.
Summary of findings and recommendations

The following recommendations and points to note emerged from these roundtable discussions on establishing a national registry for **orthopaedic devices** in Singapore.

- To ensure that the national registry is correctly designed and will remain useful and relevant in the future, its purpose and objectives must be determined at the outset (e.g., monitoring device safety and quality, to track and trace patients, to study outcomes, for regulatory purposes, or to facilitate the publication of findings).

- A minimum dataset could include patient details, device catalogue and batch number, centre, type of surgery, the surgeon’s name, and whether or not a primary revision has taken place.

- The opt-out system of obtaining patient consent to be included in the registry was felt to be more fair and efficient than an opt-in mechanism.

- Most successful, long-established registries around the world have been initiated, controlled and owned by clinicians or their professional societies.

- Funding is vital to registry sustainability. Funding models include levies on implant sales, subscription revenues for professional society-based registries, industry contributions, and government funding boosted by the savings in national healthcare costs that an efficient registry can deliver.

- Medical device manufacturers have clear responsibilities with respect to post-market surveillance.

The following points emerged from these discussions on establishing a national registry for **cardiovascular devices** in Singapore:

- To overcome the barriers of its small population and resistance to data sharing, Singapore could set up a national registry that also participates in international registries at the level of a specified minimum, extractable, common set of data.
  - The development of infrastructure to enable data pooling of harmonised data (or exchangeability) is critical.
  - Protocols should be designed to take into account stakeholders’ consent to data sharing, including patient consent, opt out, or some related strategy.
Collaboration will be required at national (HSA, academia and industry) and international levels (IMACS, NCDR, and the Asia Pacific Evaluation of Cardiovascular Therapies Collaboration).

- The standardisation of terms and definitions in line with the most recent Academic Research Consortium (ARC) guidelines should be considered to facilitate poolability.
- A minimum data set that includes whether major device-related procedures or catastrophic clinical outcomes (death, MI, stroke, “shockable” VT/VF, etc) have occurred.
- Data collection processes integrated with clinical work flow and ease of use as far as possible.
- The use of Unique Device Identification (UDI) for implantable devices will play a vital role in traceability, but its full potential cannot be achieved without adequate infrastructure to capture those data at the point of device use.
- To engage physicians, they must be convinced that registries are for their benefit, because the data they generate can be used to monitor patient outcomes and appropriate use criteria, to aid education and maintenance of certification, and to improve accountability.

Following are the general recommendations for designing and implementing medical device registries in Singapore that emerged from this meeting.

- Because a registry can have several purposes, and its objectives may differ for medical devices used in different medical fields, consensus must be reached from the outset on the goals and priorities of each registry, to facilitate its appropriate design and operational logistics.
  - The categories of devices and procedures that should be included in Singapore’s registries must be prioritised by identifying medical device types for which a long-term registry will be of significant public health importance.
  - From the regulatory perspective, the ability to track and trace is key. The ability of a registry to enable effective identification of safety signals is therefore a priority.
  - Protocols to follow in the event that medical device failure or safety signals are detected must be established.
- Common demographic, clinical, procedural and device-based data elements to be used by professionals in the registry cluster should be determined.
Methodological tools/procedures for data collection should then be developed and shared, including those for long-term outcomes. Interoperability with existing electronic health records and claims data should be enhanced where possible. Data collection should be incorporated into the workflow of the clinicians or the team supporting the clinician, to reduce burden and ensure that data are uniformly collected.

Clinicians must be engaged in the process from the earliest stages to ensure the success of the registries and the usefulness of the data they will generate, as well as their buy-in regarding the sharing of relevant patient data and outcomes.

- Positive awareness campaigns can be used to educate physicians and patients about the benefits of national registries.

Registry governance structures should be adopted that promote rigorous design and compliant use, and the reporting of key findings with high transparency to relevant stakeholders such as regulators, clinicians, the public, and patients.
Introduction

The Health Sciences Authority (HSA) of Singapore is in the process of enhancing the regulatory framework for medical devices to facilitate timely approval and availability of high-risk medical devices within Singapore, whilst ensuring patient safety. The development and implementation of medical device registries for high-risk devices have been identified as an important post-market surveillance strategy.

Medical device registries are organised systems that enable the use of observational methods to study the safety and effectiveness of medical devices in real-world situations. Registries can also be used to determine the nature and frequency of reported adverse events for ‘track and trace’ purposes, and in the longer term, to monitor clinical outcomes and best practices.

The use of high-risk medical device registries by healthcare systems as a post-market surveillance tool has been successfully adopted in many countries, especially by the cardiovascular and orthopaedic specialties. Singapore can learn from the challenges and successes experienced with existing registries overseas, and thereby understand the necessary frameworks required to support the governance and implementation of medical device registries locally.

To this end, a medical device roundtable meeting was held in Singapore on 15 March 2013. The objectives were to create a platform to identify and build on best practices presented by a panel of international experts on post-market surveillance of medical devices, and to discuss the practical applications of such registries, with the ultimate goal of setting up cardiac and orthopaedic registries in Singapore. Both local and foreign perspectives and recommendations were sought from various regulatory, manufacturing, academic and clinical representatives.

Overview of medical device regulation

In her opening remarks, Guest of Honour, Dr Amy Khor, Minister of State for Health and Manpower, Singapore pointed out that the medical device sector is a key element of the
broader healthcare industry. Medical devices play a vital role in the prevention, diagnosis, monitoring and treatment of disease. With the world’s top ten medical device companies having established regional headquarters in Singapore, research and development in this field is progressing rapidly. To keep pace with these rapid technological advances and to meet the increasing demand for medical devices, it is critical that Singapore continues to enhance and maintain a robust, risk-stratified regulatory framework for medical devices to safeguard patients.

Pre-market medical device regulatory controls were phased in over 5 years from 2007 to 2012 in Singapore. Using a confidence-based approach, the regulatory framework was further enhanced over the previous year to shorten review times and lower registration fees, in order to facilitate timely access of devices to the market. Singapore’s post-market controls complement pre-market product controls to ensure the continued safety of marketed devices, and these include vigilance, surveillance and compliance monitoring frameworks.

Dr Khor went on to describe the global shift towards a greater emphasis on post-market surveillance of devices, one aspect of which involves the setting up of medical device registries. For example, Canada, Australia and the UK have jointly set up an International Consortium of Orthopaedic Registries (ICOR), and Australia has a National Joint Replacement Registry (NJRR). In the US, the American College of Cardiology (ACC)’s National Cardiovascular Data Registry (NCDR) comprises a suite of registries that cover several types of cardiovascular implants and devices, and in Japan, the Japanese Registry for Mechanically Assisted Circulatory Support Model (J-MACS) is being rolled out. Hence, in line with recent global developments, the HSA is exploring the establishment of national registries for high-risk medical devices to complement its pre-market regulatory controls. Dr Khor highlighted that effective post-market surveillance through initiatives like registries not only serves an important regulatory function, but is also an integral component of good industry practice. Medical device registries allow companies to benefit from an enhanced understanding of the performance of their devices in the market, which in turn enables further refinements in quality. Clinicians also gain from evidence-based information that can help to improve the quality of patient management.

Because of the wide-ranging nature of post-market surveillance, it is important for the various stakeholders to collaborate and cooperate in establishing effective device registries.
Active involvement by a network of different stakeholders will greatly enhance the eventual reach and strength of the system.

**Engaging stakeholders to enhance post-market surveillance**

Associate Professor John Lim, Chief Executive Officer of the HSA, pointed out that since 2007, when Singapore’s first phase of medical device regulation was implemented, HSA has endeavoured to engage a diversity of stakeholders. These include representatives of the medical device industry and associations, hospital purchasing departments, academia, and healthcare professionals. He emphasised that, given the relatively short history of medical device regulation locally and globally, the HSA considers it critical to foster and develop a robust medical device regulatory system that involves all key stakeholders.

Under Singapore’s current framework, after a medical device has been registered and marketed, post-market device-related adverse events are monitored through both mandatory reporting by the industry, and voluntary reporting by healthcare professionals. However, challenges remain regarding the tracking of real-time performance, and the benefits and risks of medical devices after they enter the market, especially for implants. This is further hampered by the lack of a unified code for devices that can enable rapid identification of devices and patients in whom they have been implanted.

A key strategy to enhance post-market medical device surveillance in Singapore therefore involves the development and implementation of medical device registries. These registries would enable stakeholders to collect and maintain systematic records on devices for specified time periods and populations with respect to disease areas, medical conditions or procedures. This will in turn help to ensure prompt identification and traceability of faulty devices to facilitate recalls or other relevant corrective actions. In addition, information from these registries could be used by device manufacturers to facilitate the development of new devices and/or new indications of existing devices. Examples of successful registries established to date include the ACC’s NCDR, J-MACS, and the Australian Orthopaedic Association National Joint Replacement Registry (AOA NJRR).
Professor Lim admitted that, while it is not possible to identify all potential problems or issues by analysing data from device registries, they are nonetheless effective in helping to increase the discovery of systemic device issues or safety signals that may not otherwise be detected. One example is the recent case of complications with metal-on-metal hip implants. Data from the AOA NJRR and the UK’s National Joint Registry (NJR) enabled the detection of signals that led to the identification of high failure rates associated with the metal-on-metal prostheses, resulting in their subsequent withdrawal from the market.

To discuss these issues, Professor Lim welcomed to this inaugural Roundtable regulatory experts from some of the HSA’s key partner agencies, including the UK Medicines and Healthcare products Regulatory Agency (MHRA), the Australian Therapeutic Goods Administration (TGA), and the Japanese Pharmaceuticals and Medical Devices Agency (PMDA). He also welcomed the renowned local and international clinical experts, academics, and members of the medical device industry who attended this roundtable event. He expressed the hope that the ensuing presentations and discussions would enable participants to learn from each other about the issues, challenges and best practices regarding the existing registries globally, and to adapt the latter to develop local device registries. The ultimate goal, he concluded, will be to establish medical device registries that are not only relevant for Singapore, but that will also strengthen global coordination amongst different registries for devices used in the same clinical specialties.

The need for medical device registries

An overview of the scope of available medical devices formed the opening remarks of symposium co-chair Professor Ranga R Krishnan, Dean of the Duke-NUS Graduate Medical School in Singapore. In Singapore, 810 orthopaedic devices and 980 cardiovascular devices have been approved, out of which 730 and 370 devices are implantable devices, respectively.

Orthopaedic and cardiovascular devices make up 18% and 22%, respectively, of all registered class C and D devices in Singapore. With regard to the registered companies that import these devices into Singapore, multinational companies account for 37% and 48% of
orthopaedic and cardiovascular devices, while small and medium-sized enterprises (SMEs) account for 63% and 52%, respectively.

In summary, a vast range of devices is available, many of which remain within a patient’s body for a long time. Similarly, many companies manufacture these devices, globally and locally. No medical device is free of risk, and clinical data from pre-market studies is limited in duration and scope. In the event that a performance problem is identified, traceability is key. It is vital to know not only which patient has received a particular device, but also the device’s manufacturer and batch or lot number. Given the number of adverse events that can be associated with it (Table 1), the need to monitor adverse events and outcomes associated with a particular device, and the ability to trace a patient or manufacturer if required, become obvious. As the world’s population ages and more devices are implanted, requirements for traceability will only increase.

Table 1. Adverse events associated with medical devices

<table>
<thead>
<tr>
<th>Orthopaedic implants (knee, hip replacement)</th>
<th>Cardiovascular implants (stents)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Delayed- or non-union of implant</td>
<td>• Angina/coronary ischaemia</td>
</tr>
<tr>
<td>• Loosening, disassembly, bending or fracture of implant</td>
<td>• Arterial aneurysm or rupture</td>
</tr>
<tr>
<td>• Infection</td>
<td>• Atheroembolisation</td>
</tr>
<tr>
<td>• Excessive wear</td>
<td>• Infection / abscess formation at access site</td>
</tr>
<tr>
<td>• Pain</td>
<td>• Ischaemia requiring intervention</td>
</tr>
<tr>
<td>• Dislocation</td>
<td>• Myocardial infarction</td>
</tr>
<tr>
<td>• Cardiovascular disorders and thromboembolic disease, including venous thrombosis, pulmonary embolus, and heart attack</td>
<td>• Stent migration / strut fracture</td>
</tr>
<tr>
<td>• Tissue reactions, osteolysis, and/or implant loosening caused by metallic corrosion, allergy, wear debris or loose cement particle</td>
<td>• Stroke or death</td>
</tr>
<tr>
<td>• Implant material sensitivity, or allergic reaction to a foreign body</td>
<td>• Calcification</td>
</tr>
<tr>
<td>• Nerve damage due to surgical</td>
<td>• Thrombosis</td>
</tr>
</tbody>
</table>

| and cardiovascular disorders and thromboembolic disease, including venous thrombosis, pulmonary embolus, and heart attack |
| Spinal implants (spinal cages) | Implantable defibrillators or pacemakers (including leads) |
| • Nerve damage due to surgical | • Inappropriate shocks             |
| | • Potential mortality due to inability to defibrillate |
| | • Constrictive pericarditis or endocarditis |
| | • Death |
| | • Fibrillation or other arrhythmias |
trauma or presence of the device

- Vascular damage, which could result in catastrophic or fatal bleeding
- Erosion of vessels and catastrophic bleeding in the later postoperative period caused by malpositioned implants adjacent to large arteries or veins
- Dural tears during surgery resulting in need for further surgery for dural repair, a chronic CSF leak or fistula, and/or possible meningitis
- Paralysis
- Death
- Spinal cord impingement or damage

- Heart wall or vein wall rupture
- Infection
- Lead abrasion or insulation damage and discontinuity
- Lead migration/dislodgment
- Muscle and/or nerve stimulation
- Myocardial damage or irritability
- Poor connection of the lead to the device, which may lead to oversensing, undersensing, or a loss of therapy

**Heart valves**

- Compression of conduit between the heart or ascending aorta and the sternum
- Graft kinking; excessive bleeding through wall of graft
- Bleeding diatheses
- Progressive neointimal thickening and peeling within the graft
- Progressive stenosis and obstruction of the valve and/or graft
- Graft infection and endocarditis
- Regurgitation, haemolysis, and malfunction of the valve due to distortion at implant
- Tissue deterioration including infection, calcification, thickening, perforation, degeneration
- Heart failure, cardiac failure, and myocardial infarct

In Singapore at present, data on implanted medical devices are kept by individual institutions. These are often manually completed, paper-based records that include the patient’s particulars, type of surgery, device type or label sticker, and the identity of the physician who implanted the device. These data may not even be stored in a common location within each institution, nor can they be accessed easily by other institutions. There is also no established process for handling the data, such as consistency in the length of time for which these data are stored – it can range from 3 to 5 years, after which records are usually discarded. Patients’ identities are also sometimes provided to vendors for billing purposes.

Therefore, there exists a clear need for medical device registries of orthopaedic and cardiovascular devices in Singapore, concluded Professor Krishnan, and these registries must be simple, easy to use, and form a component of the normal clinical work flow.
Registry uses: Keynote lectures

Using registries for evidence appraisal – US experience

The opening remarks by co-chair Professor Mitchell Krucoff, Director of the Cardiovascular Devices Unit at Duke Clinical Research Institute, built on Professor Krishnan’s remarks by demonstrating the value of existing registries in the US. He pointed out that international device registries can transcend geographic, professional and conceptual boundaries between stakeholders, and open the door to public-private partnering to achieve solutions that no single stakeholder can.

The main function of registries is to enhance the ability to collect and pool data on adverse events, Professor Krucoff emphasised. If every nation, specialty and entity were to collect its own registry data individually, each database could be underpowered to detect, with any statistical certainty, whether or not safety events are occurring. Enhanced detection of safety signals not only promotes patient well-being, but also serves as an important target for the design and manufacturing of better and safer devices. Therefore, it is important for registry owners to explore ways of collaborating and sharing their data for stakeholders to gain the most value from the registries.

Objectives and infrastructure are both important aspects of registries (Table 2). In addition, on-going sustainable electronic registries provide important infrastructure in the form of operational electronic data capture with quality controls that apply standardised definitions over multiple observations. They can also provide users with consistent case report forms (CRF) as data-entry user interfaces.
Table 2. Important aspects of registries

<table>
<thead>
<tr>
<th>Content</th>
<th>Infrastructure</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Non-randomised longitudinal data capture</td>
<td>• Installed, operational electronic data capture</td>
</tr>
<tr>
<td>• Enable retrospective analyses:</td>
<td>• Quality controls</td>
</tr>
<tr>
<td>– Generate hypotheses</td>
<td>• Standardised definitions</td>
</tr>
<tr>
<td>– Confirmatory evidence</td>
<td>– Consistent case report forms</td>
</tr>
<tr>
<td>– Observational analyses</td>
<td>• Clinical and research applications</td>
</tr>
<tr>
<td>– Safety signal detection</td>
<td>• Provide abundant electronic information that can be used for:</td>
</tr>
<tr>
<td>– Integrated Development Environment (IDE) extension</td>
<td>– Prospective randomised controlled trials</td>
</tr>
<tr>
<td>– Pre-market approval (mature devices)</td>
<td>– Prospective single-arm studies</td>
</tr>
<tr>
<td></td>
<td>– Adaptive designs</td>
</tr>
<tr>
<td></td>
<td>• IDE</td>
</tr>
<tr>
<td></td>
<td>• Pre-market pivotal studies</td>
</tr>
<tr>
<td></td>
<td>• Post-market extension studies</td>
</tr>
</tbody>
</table>

Professor Krucoff went on to describe how existing registries provide vital collaborative and data collection opportunities. The Medical Device Epidemiology Network Initiative (MDEpiNet)\(^1\) in the US is part of the Epidemiology Research Program at the US FDA’s Center for Devices and Radiological Health (CDRH). This initiative is a collaborative programme, through which the CDRH and external partners (medical device industry, professional societies and patient advocates) share information and resources to enhance the understanding of the safety and effectiveness of medical devices after they are marketed.

An example of such an initiative in the public health domain is an on-going prospective randomised clinical trial that utilises electronic registry infrastructure, the Study of Access Site for Enhancing Percutaneous Coronary Intervention (PCI) for Women (SAFE-PCI for Women). This study in the field of interventional cardiology is designed to determine why women suffer more bleeding and more vascular complications than men. Women

\(^1\) [http://www/fda.gov/MDEpiNet](http://www/fda.gov/MDEpiNet). MDEpiNet aims to develop new ways to study medical devices that improve the understanding of their safety and effectiveness throughout their life cycle by bridging gaps in evidence, developing datasets and creating new methods of conducting robust analytic studies.
undergoing urgent or elective PCI are randomised to receive catheterisation either through the femoral artery in the leg, or through the radial artery in the wrist (the latter technique has been shown to reduce bleeding complications in general). This trial, in partnership with the ACC’s NCDR,\(^2\) includes only centres in the US that are already entering 100% of their PCI data into the ACC NCDR’s CathPCI registry.\(^3\) Hence, all key patient descriptors (age, gender, concomitant medications, procedural details from the PCI itself, and index hospitalisation adverse endpoints) have already been entered for all patients by each of these participating hospitals.

Using a small grant from the National Institutes of Health (NIH), the National Cardiovascular Research Infrastructure\(^4\) was developed for this project as a means of electronically reaching into the NCDR electronic data stream for each participant in the study. In other words, all the data that have already been entered into the NCDR can be used to populate a Part 11-compliant database, without re-entry of any data being required. The result is a 65% reduction of the site coordinator’s workload per patient, compared to other similarly designed clinical trials. In the US, using a CFR Part 11-compliant database, the cost of a new device submitted thorough the Investigational Device Exemption (IDE) would be reduced by approximately 35% using this mechanism, because the data have already been entered by the participating hospitals.

Safety concerns over the course of the total product life cycle can also be more accurately, efficiently and continuously monitored if the same data endpoints are used from the very first use of the device in humans, through randomised trials, to the post-market environment. This process will enhance the speed and reduce the cost of pre-market randomised trials, while increasing the quality of post-market surveillance by providing the denominator in addition to uniformly defined safety observations.

\(^2\) https://www.ncdr.com/webncdr/home/
\(^3\) https://www.ncdr.com/webncdr/cathpci/. The CathPCI Registry assesses the characteristics, treatments and outcomes of cardiac disease patients who receive diagnostic catheterisation and/or PCI procedures.
\(^4\) https://www.ncrinetwork.org/. National Cardiovascular Research Infrastructure (NCRI) is a partnership between Duke Clinical Research Institute and the American College of Cardiology Foundation to develop a clinical investigator network based on the data collection activities of the NCDR. The NCRI unites sites with resources for site recruitment, education, data collection, data standards, and guideline development so that large, simple clinical research projects can be efficiently executed.
Using registries to strengthen post-market surveillance – UK experience

Mr John Wilkinson, Director of Medical Devices at the UK’s MHRA, provided an overview of how registries are used in the UK to strengthen post-market surveillance. He pointed out that real-life information about clinical practice is required by numerous stakeholders:

- clinicians – to inform clinical choices around interventions and outcomes
- Health Technology Assessment (HTA) – to inform economic decisions
- industry – to inform decisions on safety, portfolio management, and research and development
- regulators – to inform decisions on safety and effectiveness
- patients – to understand any emerging risks of medical devices that they have received.

At present, Unique Device Identification (UDI) markers and electronic patient record-keeping are being used in the UK, but the ability to link the two datasets consistently and effectively is still lacking. Of the range of different tools that can be used for post-market surveillance, Mr Wilkinson stated that registries offer the best source of concrete data that can be used to make validated, rather than opinion-based, decisions.

The National Joint Registry (NJR)⁵ of England, Wales and Northern Ireland, which is currently the world’s largest joint registry, collects information on joint replacement surgery and monitors the performance of joint replacement implants on all hip, knee, ankle, elbow and shoulder joint replacements across the UK’s National Health Service (NHS) and private healthcare sector. Mr Wilkinson stressed that a registry’s size is very important in providing enough statistical power for signal detection. In 2012 alone, the NJR collected statistics on a total of 181,144 completed operations: 127,978 under the NHS and 53,218 in the private sector.

The NJR produces extensive reports that not only provide useful denominators, but also impact clinical practice and social policy issues. Hip replacement procedures have changed since 2005 as data emerged about safety and outcomes. Data from the NJR have also shown that the Body Mass Index (BMI) of UK’s hip replacement patients has steadily increased since 2004 in both males and females, and that there is a relationship between

BMI and the success of the implant procedure. As a result, changes in health and social policies may follow. Finally, the NJR has helped to identify medical centres that have outlier revision rates.

A key lesson learned in the UK is that clinicians should be the key drivers of the registries because they are the primary sources of data input, by coming into contact with the affected patients on a regular basis. Thereafter, expert analysis of registry data, which must be funded as part of the system, could be jointly conducted by the clinicians, industry (as part of their post-market surveillance) and regulators. It is crucial that registries are effectively supported by the industry. Duplication of data can only be avoided if data arising from the registries are shared, and there is a definite need for registries to go beyond just one country and extend their reach into the wider geographical region. At present, the UK pools drug-related data with Denmark to enable enhanced signal detection.

With regard to registry governance, clear rules must be established around who receives what information, and when and how that information is used, because transparency is an important aspect of registry. It is vital that the data collected by the NJR are effectively communicated to the most relevant stakeholders such as clinicians, the public, and patients, in the form of Annual Reports and Patient Guides. Issues may arise when patients are asked to provide their consent to being part of a registry. In the UK, a breast implant registry established in the early 1990s failed because most patients refused to give consent to be included in the registry.

Cost versus benefit is another important issue. The NJR costs around US$ 4.5 million to run annually, and it is questionable whether it’s funding model, which involves a levy on all medical device sales, is sustainable. In addition, numerous learning curve issues can arise, so time-to-usefulness of data must be calculated. In the UK, it took 6–7 years before data from the NJR could be used to its best advantage. UDI is absolutely critical, and must be aligned with effective data collection mechanisms that are practical for clinicians to use in a hospital environment. Systems that are functional both locally and nationally must be set up.

Reiterating his emphasis that for a registry, size does matter, Mr Wilkinson explained that the more data points that are available, the better, in order to provide more granular and more effective information. However, this must be balanced against the fact that the more
data points there are, the more difficult it becomes to persuade clinicians to provide them in full. He concluded that, to optimise medical device registry, effective international collaboration is vital because it can be complex, expensive and inefficient to operate a registry in isolation.

In conclusion, Mr Wilkinson took the view that public authorities should encourage registries, but not necessarily mandate them.

**U.S. FDA strategies to improve medical device post-market surveillance**

Dr Thomas Gross, Director of the Office of Surveillance and Biometrics at the CDRH, delivered his presentation via a pre-recorded video. He presented the U.S. FDA’s draft plan for strengthening the US national system for medical device post-market surveillance, which was issued in September 2012 following a 2011 recommendation by the Institute of Medicine that the FDA should develop a more comprehensive medical device post-market strategy. The current system is inefficient, costly and slow, so patients are needlessly exposed to preventable adverse events. Mandated manufacturer studies are inefficient and expensive, and the system also fails to leverage post-market data to facilitate development of new devices and new indications for existing devices.

The FDA’s updated national system will communicate timely, accurate, systematic and prioritised assessments on device benefits and risks throughout the total product life cycle, using high-quality, standardised, structured electronic health information such as billing data, electronic healthcare records and registries. The system will identify potential safety signals in near real-time from a variety of privacy-protected data sources. It will reduce the burdensome costs of medical device post-market surveillance, and most importantly, it will facilitate the clearance and approval of new devices or new indications for existing devices.

Figure 1 shows the components that make up the planned medical device post-market surveillance system. The six sectors coloured blue depict the tools that are currently used, such as the medical device reporting system and post-approval studies. The four sectors

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shown in purple represent the four initiatives that were proposed to complement the existing tools.

These systems are needed because important differences that have implications for post-market surveillance are found between devices and drugs (Table 3). Medical devices are more heterogeneous, and may have complex components. Iterative changes may be made throughout a medical device’s life cycle and, unlike drugs, medical devices are associated with design errors, human factor issues, learning curves (particularly with implantable devices), and as yet, there is no universally accepted UDI.

Figure 1. U.S. FDA Medical Device Post-market Surveillance: Current system and proposed actions.
Blue: Existing components.
Purple: Proposed components.
Table 3. Differences between devices and drugs: implications for post-market surveillance

<table>
<thead>
<tr>
<th>Devices</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Heterogeneous</td>
<td>• Homogeneous</td>
</tr>
<tr>
<td>• Complex components</td>
<td>• Pure molecules</td>
</tr>
<tr>
<td>• Iterative changes</td>
<td>• No changes</td>
</tr>
<tr>
<td>• Malfunctions</td>
<td>• Drug quality problems</td>
</tr>
<tr>
<td>• Design error</td>
<td>• No equivalence</td>
</tr>
<tr>
<td>• Human factors</td>
<td>• Straightforward use</td>
</tr>
<tr>
<td>• Learning curve</td>
<td>• National Drug Codes</td>
</tr>
<tr>
<td>• Currently no unique identifier</td>
<td></td>
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</tbody>
</table>

Components of the current U.S. FDA post-market surveillance system

To put the need for new tools into context, Dr Gross described the US FDA’s current surveillance system. The current device surveillance landscape includes passive and enhanced reporting systems. The main passive system is the Medical Device Reporting (MDR) system. The U.S. FDA receives several hundred thousand individual reports per year (e.g., more than 500,000 in 2012). Over 95% of these reports come from manufacturers and include device-related deaths, serious injuries and malfunctions.

Another national reporting system is the Medical Product Safety Network (MedSun), which provides enhanced surveillance in the form of a two-way communication channel between the U.S. FDA and a nationwide network of 275 hospitals. This provides good insight into how devices are used in a hospital setting, as well as reports on device failures. This network can be used to carry out surveys and targeted clinical research, and focus on individual devices of interest, such as electrophysiology devices. Both the passive system and the enhanced MedSun system help the U.S. FDA to address issues such as out-of-box failures, software glitches, and manufacturing defects.
Other tools in the U.S. FDA’s current post-market system include:

- post-market studies – mandated for manufacturers of class III high-risk devices (250 studies\(^7\) are on-going)
- Section 522 studies – ordered when a public health issue is discovered in the post-market period for class II or III devices (~ 250 on-going studies for 12 device types\(^8\))
- discretionary studies – use a variety of data sources such as registries, claims data and electronic health records to monitor device performance, investigate adverse events, and characterise benefits/risks in patient sub-groups
- literature searches and systematic reviews
- compliance tools such as recalls, seizures and injunctions.

The U.S. FDA’s Sentinel Initiative, which was mandated by Congress in 2007, is also very important for active surveillance. The Sentinel Initiative uses large distributed data sources for active surveillance purposes. These data sources are mostly claims-based or billing data sources, augmented by electronic healthcare records. This effort is primarily drug-focused, simply because these data sources can currently only uniquely identify drugs, but not devices. At present, the Sentinel Initiative can access information on more than 120 million patient records, which are privacy-protected. Once UDIs are incorporated into these data sources, the Sentinel Initiative will be expanded to include medical devices. Robust registries that can be linked to these Sentinel Initiative data sources can then be developed.

**Limitations of the current system**

The tools described above often fail to yield quality data in a timely fashion. This is particularly the case with the MDR passive surveillance system. Available data are often insufficient for regulators’ needs because they lack critical information about device manufacturer, make and model. Many data sources do not have longitudinal follow-up – in many registries, follow-up ends after 30 days. The collection of required post-market data may also be inefficient, particularly in the case of de novo post-approval studies or condition-of-approval studies. Finally, the current tools are rarely leveraged for pre-market uses.

\(^7\) [http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma_pas.cfm](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma_pas.cfm)

New initiatives

As shown in Figure 1 above, four initiatives have been proposed to develop a more comprehensive post-market surveillance system:

1. Establish a UDI system and promote the incorporation of UDI into electronic health information.
2. Promote the development of national and international device registries for selected products.
3. Modernise adverse event reporting and analysis.
4. Develop and use new methods for evidence generation, synthesis, and appraisal.

Dr Gross showed an example of device packaging bearing a UDI, represented by linear barcodes (Figure 2). The UDI is alphanumeric and will capture in one part the manufacturer’s make and model, and in another part, production identifiers such as lot number or serial number, again represented by a barcode and the alphanumerics below the barcode. These labels should be machine-readable as well as human-readable.

Dr Gross emphasised that establishing a UDI system and promoting its incorporation into electronic health information will truly transform surveillance by providing standard and specific ways to document devices in records. UDI will enhance surveillance capabilities on several fronts, such as reporting on and detecting adverse events and product problems, reducing medical errors, and generating evidence to assess benefit and risk profiles. A rule mandating UDI is expected in 2013. The U.S. FDA is developing a global unique device identification database, which will be operational in time for the ruling.
The second initiative, i.e. the development of national and international device registries, was the subject of this medical device roundtable. Medical device registries allow the capture of critical data about the patient, the device and the implant procedure, and these can be linked to longer-term outcomes. The U.S. FDA currently uses registries for a number of reasons, including assessing real-world device performance. The FDA has facilitated and fostered the development of over two dozen device registries in the past five years, as well as registry consortia.

Issues remain regarding inefficiencies and burdens in registry development and maintenance, so the leverage of existing experience and expertise can only help to facilitate registry development. Dr Gross highlighted the following points that are critical to planning the optimum medical device registry:

- Establish common demographic, clinical, procedural and device-based data elements that can be used across all registries.
- Develop and share methodological tools for data collection, including longitudinal outcomes.
- Enhance interoperability with electronic health records and claims data.
- Develop criteria that, from the U.S. FDA’s perspective, would render a registry eligible to support a U.S. FDA-required post-approval study (i.e. to embed that post-approval study in a registry).
- Identify priority medical device types for which the creation of a longitudinal registry is of significant public health importance.
- Adopt registry governance structures that promote rigorous design and use and the reporting of key findings with high transparency.

The third initiative involves modernising adverse event reporting and analysis, which currently suffers from underreporting, inefficient reporting, and a lack of timeliness in receipt and analysis, through the following actions.

- Develop an automated adverse event reporting system.
  - The U.S. FDA is currently piloting the use of triggers for automated reporting in electronic health records. For example, with regard to coronary stents and thrombosis, software capabilities are embedded in structured electronic healthcare records so that when a thrombosis event occurs and is linked to a coronary stent, an adverse event reporting form can be auto-populated with the information from the electronic healthcare record, and can automatically be sent to the U.S. FDA as an MDR report.

- Increase the number of medical device reports received electronically.
  - Currently, 75% of reports are received electronically, and these are voluntarily submitted from low- and large-volume reporters. Mandatory electronic reporting is currently under consideration.

- Develop a mobile application for adverse event reporting.
  - Planned for implementation in 2013, this would facilitate voluntary reporting by healthcare providers and patients. Initially, it will be implemented on smartphones, but the FDA hopes to extend it to other mobile platforms in the coming years.

- Modernise the medical device adverse event report database.
  - The existing database dates back to the 1990s and is unable to handle the large volumes and complexity of information currently received. A U.S. FDA Adverse Event Reporting System for devices may be in place by the beginning of 2014.

- Rapidly identify safety signals.
  - The use of automated and non-automated software-based analytic methods is being explored, to discover patterns of unexpected events amongst the hundreds of thousands of reports received annually. The use of semantic text-mining applied against internal, varied, pre-market and post-market data sources is also being explored to identify potential safety signals.
The fourth initiative involves developing new methods for evidence generation, synthesis and appraisal, based on MDEpiNet and the Sentinel Initiative, and complemented by registry development and UDIs. Evidence synthesis is made easier by the use of common data standards, and the U.S. FDA hopes to incorporate these in the development of their national surveillance system. The U.S. FDA has also been working on developing an automated signal detection system for active surveillance, namely the use of software-driven statistical algorithms to explore signal detection capabilities in large registries. The U.S. FDA hopes to extend these into integrated registry electronic health record (EHR) environments and national registries. Proof-of-concept studies for active surveillance purposes have shown promise for the use of these automated capabilities.

Dr Gross concluded with the remark that post-market surveillance presents unique challenges, but the U.S. FDA’s efforts to improve their current system will be collaborative and transparent, both domestically and internationally.
Session 1: Orthopaedic device registry

Session objectives

During the first of two sessions that focussed on orthopaedic and cardiovascular medical device registries, respectively, roundtable participants were presented with the academic, manufacturers', and clinical perspectives on medical device registries, to facilitate the final discussions on how to establish these registries in Singapore.

This session’s objectives were to:

- provide perspectives from regulators, academics, industry and healthcare professionals on orthopaedic device registries
- explore the use of registry data for pre-market applications and post-market surveillance
- present information about the AOA NJRR
- discuss development and implementation of infrastructures for orthopaedic registries
- discuss innovative approaches to registries
- discuss the role of industry in public-private partnership for building global medical device epidemiology and surveillance capabilities
- emphasise the benefits and impact of a medical device registry on healthcare systems, public health and industries.

Academic perspective: The advantages of a joint registry versus clinical trials

Professor Stephen Graves, Chairman of the AOA NJRR and ICOR, compared and contrasted the advantages of joint registries with clinical trials in arthroplasty. Using the AOA NJRR\(^9\) as an example, he demonstrated how the information they yield is very different.

According to Professor Graves, registries serve as continuous quality assurance programmes that are integrated into healthcare systems. They are designed and governed to bring about significant improvements in health outcomes. Their purpose is to collect high-

\(^9\) https://aoanjrr.dmac.adelaide.edu.au/
quality community-based clinical evidence that can be used to identify outcome differences (best and worst practice) within the relevant healthcare setting, and to subsequently provide that information to the appropriate stakeholders to enable action and beneficial change. He emphasised that one of the important characteristics of registries is that they allow the detection of differences in multiple outcomes.

Professor Graves presented some examples of data obtained from the AOA NJRR. New prostheses inserted between 1st January 2003 and 31st December 2007, which included more than 100 procedures performed with more than 1 year of follow up, were compared to the three best-performing prostheses in the same category that had well-established use within the community (over 500 procedures), and good outcomes over 5 years of follow-up. It was found that almost 30% of the new devices for hip and knee performed less satisfactorily than the three existing prostheses. In other words, had the regulatory body not approved any hip or knee replacements for use within the country during 2003–2007, patients would have been better off.

Registries can also provide information about surgeons’ performance. Data in Australia show that the number of surgeries performed by a surgeon has a small impact on joint replacement revision, if a well-performing prosthesis is used. However, if a poorly performing prosthesis is used, poor results are obtained (i.e., increased revision surgery rates), regardless of how many surgeries the surgeon has carried out. Data on the bearing surface of an orthopaedic device are easily collected from registries, and the Australian registry played a prominent role in identifying that a large-head metal-on-metal bearing surface was associated with a substantially higher risk of revision surgery. A whole class of exchangeable femoral necks was shown by the registry to have a higher rate of revision than were fixed necks, while modified polyethylene was shown to be very effective at reducing the risk of revision in hip replacement.

Professor Graves made the important point that none of this information could have been provided by clinical trials, because it emerged from community-based analyses, included entire prosthesis classes, and was not hypothesis-driven. Clinical trials are designed to prove hypotheses; they must limit confounders and attempt to reduce bias. They have predetermined site and surgeon involvement, surgical techniques and prostheses, and patient-specific inclusions and exclusions. Trials are also undertaken for a limited time, and
knowledge-dependent assumptions are critical to their design. Clinical trials are designed in such a way that a safety signal or effect can be missed if incorrect assumptions are initially made, whereas an arthroplasty registry is an on-going quality assurance mechanism that has no exclusion criteria.

Although it is often possible to determine causality from registries, causality is not the main focus of registries. The focus of registry analysis is to identify differences between good and faulty devices, and when these are identified, subsequent analysis is undertaken to identify the factors associated with these differences. A registry also enables continual monitoring of the outcomes that result from changing practices. Additionally, when a registry identifies a signal of interest, it allows one to see the impact that identifying the issue had, through the subsequent changes made, once that information becomes available to stakeholders.

Clinical trials in arthroplasty have several disadvantages. Implementation can be complex and they are expensive to run. Usually, only small numbers of patients are involved and the trials have the capacity to answer limited specific questions. Necessary study design restrictions limit wider relevance and applicability, and delays before data become available are considerable. Finally, they are subject to data interpretation bias and potential conflicts of interest from the manufacturers and healthcare professionals.

By contrast, an arthroplasty registry is simple to design, inexpensive to run and involves large numbers of patients. It has the capacity to answer many questions simultaneously. The data generated have wide applicability and relevance, and require little to no interpretation. Importantly, the information provided is independent, and there is accountable governance with no conflicts of interest. Arthroplasty registries also play a critical role in improving the outcome of joint replacement surgery. They enable surgeons to identify best practice that is relevant to their own approach to arthroplasty, and to compare simultaneously the effect of multiple factors on outcome. They are known to change practice in a beneficial manner.

The purpose of clinical evidence is to identify and enable the implementation of best practice as well as to ensure continuous improvement of clinical outcome. As to whether registries are effective from this perspective, Professor Graves showed that in Australia, the burden of revision surgery has decreased significantly since the NJRR was introduced. Revision rates for hip procedures have decreased as a proportion of all hip procedures from 14.8% to
11.2% and revision rates of all knee procedures have decreased from 10.4% to 8.8%. The resultant savings amount to $250 million, while the AOA NJRR costs just $2 million annually to run, resulting in a considerable cost-benefit ratio.

In summary, a well-run joint registry shows considerable advantages over clinical trials when it comes to cost-saving, implementing best practice and improving outcomes for patients. The ability to extrapolate data from other registries can be useful, but to enhance the precise understanding of the outcomes and experiences with orthopaedic medical devices in Singapore, Professor Graves emphasised that Singapore will be required to develop its own registry.

**Regulatory perspective: Using registries for total product life cycle appraisal**

Dr Jane Cook, Head of the Office of Product Review at the TGA of Australia, built on Professor Graves's presentation by providing more details on how the AOA NJRR functions, and how the TGA uses NJRR data.

Within the AOA NJRR, information is collected on almost every joint replacement operation that is undertaken in Australia, with the exception of those patients who chose not to have their information collected via an ‘opt-out’ system. A small amount of confidential information is collected for tracking purposes, such as patient details, reason for surgery, and whether the surgery was to the left or right hip or knee. Information on the type of joint replacement and the individual components used in the operation are also collected.

If a revision occurs, the AOA NJRR records details about the revision procedure and links it to the first (or primary) operation. This enables the AOA NJRR to provide information about which primary procedures have been revised at any time, the reason for the revision, how long after the original surgery the revision took place, and which of the components were replaced.
The registry has several benefits from a regulatory perspective. A wide variety of analyses is possible, notably Kaplan-Meier survivorship, and revision rates among particular patient populations, facilities, surgeons, implant types and implant models. Because of the ‘opt out’ method of enrolment, the data are more complete than they might be if a method involving personal reporting of replacement surgeries was used. Patients can also be tracked over time.

Individual prostheses that have a statistically significant higher rate of revision that are more than twice that of all other prostheses in the same class are identified by the AOA NJRR as being “prostheses that have higher than anticipated rates of revision”. There may be many reasons for increased revision rates. These reasons may not be related to the identified implant (e.g. high rates of infection) or specific to the identified implant (e.g. metal-on-metal component wear). The implants may also have redeeming features that make the higher revision rate “tolerable”. Nevertheless, the differences are statistically significant, and, using the criterion of twice the revision rate of other similar implants, these implants can be identified as outliers that warrant further investigation.

The AOA NJRR also publishes various comprehensive performance reports annually, including both hard copy and online-access versions, as follows.

- An Annual Report, published in October each year on the outcomes of hip and knee replacements. Findings are derived from analyses of data collected between 1999 until the December of the year prior to the publication of the Annual Report.
- Four supplementary reports on hip and knee replacement: Demographics of Hip Arthroplasty; Demographics of Knee Arthroplasty; Mortality of Hip and Knee Arthroplasty and Cement in Hip and Knee Arthroplasty.
- Four supplementary reports on demographics and outcomes of shoulder, wrist, ankle, and spinal disc arthroplasty.
- Investigations of prostheses that are associated with higher than anticipated rates of revision (since 2010).
- *Ad hoc* summary reports from the AOA NJRR online database.
The registry does have limitations from a regulatory perspective. Regulations regarding privacy prevent the identification of patients, surgeons or facilities, and the data may be used to track patients only in exceptional circumstances. Furthermore, there is evidence that some reasons for revision are not being coded accurately (e.g. the terms loosening/lysis, pain, and metal sensitivity are often used interchangeably).

There can be many reasons why an individual prosthesis has a higher rate of revision, only some of which are related to the prosthesis. For regulatory purposes, the TGA uses AOA NJRR data as follows. Rather than immediate regulatory action, identification by the AOA NJRR initiates a process whereby the TGA assesses each of the individually identified prostheses to determine if their safety and performance is acceptable. This process has three stages:

**Stage 1:** The Sponsor/Manufacturer is contacted and invited to make a submission in relation to the safety and performance of the implant, and to provide:

- a summary of the types of problems, complaints and adverse event reports received about the implant to date
- the number of implants supplied, and the number of reports of revisions received by the manufacturer
- details of results of clinical trials, clinical studies or information from other registries about the safety and performance of the implant.
- an explanation for the seemingly high revision rate being experienced in Australia
- a detailed description of any design changes that have been undertaken to address the revision rate
- an outline of the perceived benefits of using the implant that may compensate for an elevated risk of revision.

**Stage 2:** An Orthopaedic Expert Working Group (OEWG) is convened to consider the NJRR data and the company’s submission. The OEWG was formed in 2007 to advise the TGA on the safety and performance of orthopaedic implants that have higher than anticipated revision rates, and major specific orthopaedics-related issues, such as the metal-on-metal implants issue. The group comprises eight hip, knee and shoulder surgeons, and one general surgeon who acts as the chairman. For every implant that is ‘identified’ by the AOA NJRR, the OEWG will consider:

- the comprehensive implant analysis provided by the AOA NJRR
any submission provided by the manufacturer
a summary report prepared by the TGA.

After considering this information, the OEWG advises the TGA on whether there is compelling evidence to show that the safety and performance of the implant is acceptable.

**Stage 3:** The TGA considers all the evidence available in relation to the implants with higher than anticipated revision rates, including the OEWG advice, and makes a decision as to whether regulatory action is necessary and possible. Section 41GN of the Therapeutic Goods Act allows the Secretary of the Department of Health and Ageing to cancel the authorisation to supply a medical device, if the Secretary is satisfied that the safety or performance of that device is no longer acceptable. The process of cancellation under this clause of Section 41GN involves a complex technical and legal argument, hence the AOA NJRR data and the advice of the OEWG are central to this argument.

Data from the AOA NJRR is also used for *ad hoc* analyses during implant adverse event investigations. This allows regulators to identify a trend where a particular component works well in one combination or for a particular purpose, but may not work well in another combination or for another purpose. For example, in May 2012, the TGA received a report of a revision of a Birmingham Hip Resurfacing (BHR) acetabular cup used in a total conventional hip replacement. When used in hip resurfacing operations, the BHR cup is a very effective implant. However, investigators noticed that, when used in conventional total implants, the Kaplan-Meier survivorship curve for the BHR cup was associated with a revision rate that increased sharply three years after implantation – a fact not yet apparent from the overall revision rates associated with the implant. The manufacturer and the TGA therefore issued a Hazard Alert about the issue, and tightened the use of the device in total conventional implants.

Dr Cook concluded that implant registries, particularly those that can provide analyses on outcomes, are an invaluable tool for post-market vigilance and monitoring. She emphasised that the outcome measures of these clinical registries must be subjected to thorough clinical and technical assessment to ensure that appropriate regulatory measures are taken.
Industry perspective on registries for orthopaedic devices

According to Dr Aran Maree, Chief Medical Officer of Medical Devices and Diagnostics at Johnson & Johnson, the medical device industry strongly values and supports joint registries.

Globally, the registry movement has actively contributed to enhanced treatment standards and patient care. Dr Maree believes that a well-designed and executed registry provides all stakeholders with generalisable, real-world evidence of clinical safety and performance. To assist medical device manufacturers in conducting post-marketing surveillance activities, they systematically review, analyse and request additional data from registries. In recent years, an understanding of the value and importance of registries has grown, not only with regard to post-market activities, but also because of the ability to include data from a well-designed and executed registry in the manufacturers’ clinical evaluation reports that are distributed to regulators worldwide. Lastly, registry data supplement the manufacturers’ post-marketing clinical trial portfolio studies.

Dr Maree views joint registries and regulators as active partners with industry in managing risks. With over 40 joint registries and registry projects active globally, manufacturers require timely access to raw data or datasets through the use of a data review committee, so that they can quickly and effectively identify and analyse potential safety signals.

Opportunities to improve collaboration between registries and industry include the harmonisation of key definitions (such as ‘revision’ or ‘outlier’, because definitions of these terms can vary between registries), the implementation of minimum datasets, improved statistical tools, and greater consistency in the way in which registries report findings globally. The medical device industry would also value the development of clear consensus guidelines around rules for timely access to registry data. For some registries, it can take manufacturers 3–4 months to gain access to the required data to be analysed for potential safety signals. Patient or device function and patient-reported outcome measures are also important, but collection of these data is currently limited in many registries worldwide.
One innovative approach to collaboration between industry and orthopaedic registries is the collaboration between DePuySynthes in Australia and the AOA NJRR after it was recognised that there was limited post-market data on an innovative acetabular component made by DePuySynthes. The success of this initiative requires support from the AOA, collaboration with the NJRR, funding for the International Musculoskeletal Research Institute in Adelaide (the study’s contract research organisation), the cooperation of implanting surgeons in collecting additional data, engagement with patients to contribute health-related quality-of-life data, and transparent communication of findings to all stakeholders.

A second novel and valuable approach to the use of registries is the ‘Beyond Compliance’\(^\text{10}\) initiative in the UK. This initiative brings together industry in the form of Association of British Healthcare Industries (ABHI), the profession (i.e. the British Orthopaedic Association [BOA]), and the regulator – the MHRA. The goal of this initiative is to improve integration of data from multiple sources and to strengthen post-market clinical follow-up of Communauté Européenne (CE)-marked orthopaedic implants under the umbrella of transparent and timely peer-review. The initiative involves collaborative peer-review of clinical performance and safety data by manufacturers, independent surgeons, and the implanting surgeon. Items reviewed are imaging data, surgical notes, discharge summaries, data from the National Patient Reported Outcome Measures Programme, and NJR data. In addition, this panel reviews routinely collected and coded adverse event data from the hospitals’ episode statistics. From an industry perspective, this provides the opportunity not only to review registry data, but also to view the interpretive dataset, which provides information about any potential root cause for revisions very soon after the release of a product onto the market.

Dr Maree reiterated that industry shares with regulators and with registry authorities the common goals of improving patient outcomes and standards of care. There is much potential for further collaboration in a number of areas in order to improve further our understanding of risk factors that affect outcomes, to evaluate the performance of new implants and technologies, to seek methods to effectively compare data from different registries, and to realise greater partnership in data collection and review. In conclusion, Dr Maree agreed with previous speakers that registries will greatly improve our ability to conduct effective and efficient post-market surveillance.

\(^{10}\) http://www.beyondcompliance.org.uk/
Clinician’s perspective: Example of an orthopaedic registry in Singapore

In preparation for this symposium, Associate Professor Inderjeet Singh Rikhraj, Chairman of the Chapter of Orthopaedic Surgeons, College of Surgeons, in Singapore’s Academy of Medicine, contacted Singapore’s six public hospitals that perform orthopaedic device implantation to determine whether they use registries. Of these, three responded that they used some form of site-specific registry, and Singapore General Hospital (SGH) provided detailed information about their registry.

SGH’s hospital-based orthopaedic registry collects data on patient demographics, type of surgery (Table 4), peri-operative outcomes (length of operation and length of hospital stay), and patient-reported outcomes and satisfaction. In the near future, data collected will also include implants used during surgery, and morbidity and mortality information.

Table 4. Number of orthopaedic surgeries performed according to SGH orthopaedic surgery database

<table>
<thead>
<tr>
<th>Type of surgery</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knee Cruciate Ligament Reconstruction</td>
<td>4,789</td>
</tr>
<tr>
<td>Thoracolumbar Spine Surgery</td>
<td>23,358</td>
</tr>
<tr>
<td>Cervical Spine Surgery</td>
<td>3,624</td>
</tr>
<tr>
<td>Hip Fracture Surgery</td>
<td>640</td>
</tr>
<tr>
<td>Foot &amp; Ankle Surgery</td>
<td>6,290</td>
</tr>
<tr>
<td>Hip Arthroplasty</td>
<td>3,698</td>
</tr>
<tr>
<td>Knee Arthroplasty</td>
<td>38,316</td>
</tr>
<tr>
<td>Shoulder Surgery</td>
<td>1,793</td>
</tr>
</tbody>
</table>

Table 5 shows data that are collected with regard to each type of orthopaedic surgery carried out at SGH.
### Table 5. Data collected by surgery type in SGH orthopaedic surgery database

<table>
<thead>
<tr>
<th>Type of surgery</th>
<th>Data collected</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sports-related surgery</strong></td>
<td></td>
</tr>
<tr>
<td>Knee cruciate ligament</td>
<td>• International Knee Documentation Committee</td>
</tr>
<tr>
<td>reconstruction</td>
<td>• Tegner Score</td>
</tr>
<tr>
<td></td>
<td>• Lysholm Score</td>
</tr>
<tr>
<td>Shoulder score</td>
<td>• UCLA</td>
</tr>
<tr>
<td></td>
<td>• Constant Score</td>
</tr>
<tr>
<td></td>
<td>• Oxford Shoulder / Instability Score</td>
</tr>
<tr>
<td><strong>Spine surgery</strong></td>
<td></td>
</tr>
<tr>
<td>Cervical spine surgery</td>
<td>• North American Spine Society Assessment</td>
</tr>
<tr>
<td></td>
<td>• Oswestry Disability Index</td>
</tr>
<tr>
<td></td>
<td>• Japanese Orthopaedic Association (for myelopathy conditions)</td>
</tr>
<tr>
<td></td>
<td>• Erectile Dysfunction Index</td>
</tr>
<tr>
<td></td>
<td>• Range of Motion</td>
</tr>
<tr>
<td></td>
<td>• RAND 36-Item Health Survey 1.0</td>
</tr>
<tr>
<td>Lumbar spine surgery</td>
<td>• North American Spine Society Assessment</td>
</tr>
<tr>
<td></td>
<td>• Oswestry Disability Index</td>
</tr>
<tr>
<td></td>
<td>• Range of Motion</td>
</tr>
<tr>
<td></td>
<td>• SRS-22 (for scoliosis)</td>
</tr>
<tr>
<td></td>
<td>• RAND 36-Item Health Survey 1.0</td>
</tr>
<tr>
<td><strong>Hip Surgery</strong></td>
<td></td>
</tr>
<tr>
<td>Hip arthroplasty</td>
<td>• Western Ontario McMaster Universities Index</td>
</tr>
<tr>
<td></td>
<td>• Oxford Hip Score</td>
</tr>
<tr>
<td></td>
<td>• RAND 36-Item Health Survey 1.0</td>
</tr>
<tr>
<td>Hip fracture surgery</td>
<td>• Parker Mobility Score</td>
</tr>
<tr>
<td></td>
<td>• Harris Hip Score</td>
</tr>
<tr>
<td></td>
<td>• RAND 36-Item Health Survey 1.0</td>
</tr>
<tr>
<td><strong>Knee replacement surgery</strong></td>
<td>• Knee Society Clinical Rating Scale</td>
</tr>
</tbody>
</table>
Associate Professor Inderjeet concluded his presentation by listing the numerous publications that have been based on data from this registry, which cover all aspects of orthopaedic surgery.

**Roundtable discussion: Registries for orthopaedic devices**

Co-chaired by Professor Graves and Professor Krishnan, the purpose of this roundtable discussion session was to explore the opportunities of establishing an orthopaedic registry in Singapore, taking into account the information that had been presented. The panellists for this session are listed on page 6 of this report. The following issues were raised and debated.

**Registry design is linked to registry purpose**

It is important to determine from the outset the level of data that the orthopaedic registry will be designed to collect. A requirement for too much information becomes burdensome and leads to poor compliance, while an insufficient dataset may reduce the ability of the registry to answer questions. The AOA NJRR collects what Professor Graves described as ‘core data’ or the ‘minimum dataset’: the medical device is linked by catalogue number and lot
number to the patient; other information collected includes the centre at which the surgery was performed, the surgeon’s name, and whether or not a primary revision has taken place. According to Professor Graves, much of the information takes less than a minute to collect because device details are entered using sticker labels in a paper-based system. A paper-based system is used because it is quicker for experienced staff to enter the data using this system. In addition, hospitals are resistant to an electronic system and errors can also be introduced with an electronic system. To assess a medical device’s performance and outcomes, any information about subsequent revision surgery required by that patient can be linked in the database to the original entry. This level of data was termed the ‘minimum dataset’. According to Professor Graves, patient-reported outcomes have not contributed to improving the outcome of joint replacement surgery as collected by a registry, and are probably unnecessary. The SGH orthopaedic device registry described by Professor Inderjeet was felt to be very detailed, although obviously of great value from an academic point of view.

The most effective way to ensure that a registry is correctly designed is to determine at the outset the goals and objectives of that registry (e.g., whether it is intended to monitor device safety and quality, to track and trace patients, to study outcomes, for regulatory purposes, or to facilitate publication of findings). Professor Krucoff suggested that predictive models in the literature can leveraged when designing registries because they can inform the required ‘minimum dataset’ in a particular disease area (e.g. age, co-morbidities, likelihood of joint failure, orthopaedic device environment, use in patients who are more likely to be at a higher risk of revision surgery). When designing the registry, data collection should be incorporated into the workflow of the clinicians or the team supporting the clinician, to reduce burden and ensure that data are uniformly collected.

It is also important to design a national registry that will remain useful and relevant for years to come, and which should be able to provide more information than about safety alone. Quality of life is becoming increasingly important to patients, and as the population ages, this will be high on patients’ list of priorities.

In Australia, it was found to be essential that the registry be clinician-led and owned, and that the orthopaedic surgeons and specialists understood and agreed with the registry’s purpose and how it would benefit them in providing better service to their patients. Consumers often
also seek involvement, because they want to be notified and advised on next steps if they have received a device for which safety concerns have been raised. Traceability is therefore an important purpose of a registry. Dr Cook pointed out that it will be an interesting challenge for the doctors who established the registries to engage with the consumers who are the recipients of affected medical devices.

A registry’s intended uses will not always be consistent for the same devices in all countries, in all regions. These factors should be taken into account so that registries can be linked to others in the future if the need arises. Increasingly, data and records are being documented electronically. Current registry designs may change because of the increasing movement towards electronic documentation, to ensure that data can be mined more effectively in the future.

**Patient consent: opt-in versus opt-out**

Two methods of obtaining patient consent to be included in a registry can be used: opt-in (patients have to provide signed consent to be included) and opt-out (their details will be included unless they sign a form stating that they refuse consent). Professor Graves highlighted that the requirement for obtaining patient consent for registry inclusion is not universal. If the registry is viewed as a quality assurance activity, then many countries have the appropriate legislation that allow collection of those data without informing the patient, as long as no personal data are published and only aggregated data are subsequently published. In Australia, the opt-out mechanism is used. Of the 820,000 patients included over the 12–13 years that the registry has been running, only 26 patients have opted out across the country. In other words, patients are generally very willing to participate.

The disadvantage of an opt-in mechanism is that it introduces an additional system that must be managed, and problems with collecting the consent forms and matching these consent forms with the other data may arise. The opt-out system was approved in Australia because not only are most patients willing to participate, but also because if problems arise with processing written consent forms, people who want to participate are essentially being prevented from doing so. The opt-out system allows more people to participate, so their intention of participating is much easier to attain.
The SGH Orthopaedic registry in Singapore also uses an opt-out system. No consent forms are used; the surgeon provides the necessary data on a default screening form.

**Who should set up the registry and how can participation be encouraged?**

Attempts were made ten years ago to set up a hip and knee registry through Singapore's Orthopaedic Association under the initiative of Professor Tay Boon Keng, but the registry did not become fully operational, possibly because it was not mandatory to participate and not all clinicians in Singapore belong to the Orthopaedic Association or the Academy of Medicine.

The international experts gave the following advice. In Australia, their registry was initially motivated by the surgeons because of concerns about rates of revision, which were shown by preliminary data to be twice that of Sweden, which already had a registry. The Australian surgeons also recognised numerous advantages to having ownership of the registry. According to Professor Graves, most registries around the world that have been successful, long-established, and received cooperation from the community have, in some way, been controlled and owned by clinicians.

Mr Wilkinson pointed out that in the UK, the initiative was instigated at the behest of the UK Department of Health, but it very quickly became clear that it should be driven by the BOA.

Several strategies were suggested to encourage clinicians’ participation. One way is for the government to mandate participation. Another is to link enrolment in registries to reimbursement or payment strategies, which has worked very effectively in the US for two cardiovascular registries. Another driver of participation is to promote it as a demonstration for centres of excellence – in the US, hospitals now have to justify why they are not participating in a registry, given that other hospitals have decided to participate and demonstrate their excellence.
Funding the registry

The sustainability of a registry is important, hence sources of long-term funding must be considered. Mr Wilkinson stated that the UK’s NJR costs US$ 4.5 million annually to run. The source of this funding is a £20 levy on every unit sale in the UK. In Professor Krucoff’s experience, professional society-based registries may be driven through subscription revenue of participating members, whereas governmental models may adopt either levies or other types of fees, or fund it directly from a government budget structure.

In Australia, the government funds registries as a cost of healthcare, because of the obvious cost benefit. Professor Graves explained that the cost of running the Australia registry is $2 million per year, and the sales for hip and knee replacement in Australia total $1.5 billion dollars annually. Legislation was introduced in Australia to develop a cost recovery programme, whereby the government subsequently bills the industry for the funding of the registry on a levy-based system. For a $20,000 procedure in Australia, $20 is collected, with the added bonus that the procedure is then monitored for the patient’s lifetime.

Mr Daniel Verstappen of GE Europe Healthcare suggested that more creative solutions could also be considered, in addition to registry funding by the government or industry. For example, the AOA NJRR has resulted in cost savings of $250 million, and perhaps these savings could be used to partially fund the registries.

Addressing surgeon’s concerns

Panel members outlined the concerns that might be raised by clinicians. Because early failure following knee surgery could also be attributable to surgical technique, surgeons in Singapore might be concerned that a registry might serve as an audit of the success of their operations. Their concern is that publicly available revision rate information might influence patients’ choice of surgeons, or even lead to regulatory action being taken. They are also concerned about whether patient confidentiality might be compromised.
These concerns were addressed by the panel. Registries provide enormous benefits to surgeons, provided that mechanisms are in place to protect the surgeons’ identities. Registries can provide surgeons with vital information about patient outcomes and thus assist them to achieve better results (a registry can show whether patients have gone elsewhere for a revision, which the surgeon might not be able to determine otherwise). In Australia and other countries, registry participation is being integrated into continued professional development because increasingly, surgeons have to justify their performance. There has also been a significant shift towards a culture of greater transparency regarding individual surgeons’ performance in many countries.

Australia has quality assurance legislation in place to ensure that it is not possible to identify specific surgeons, hospitals or patients to anyone other than the individual surgeon who visits the registry to review his or her data. Professor Low Cheng Ooi also suggested the use of technology to de-identify sensitive data.

Professor Tay Boon Keng pointed out that clinicians might also query whose responsibility it is if an implant fails – theirs or the manufacturer’s. They have a strong desire for proper protocols to be developed for notifying affected patients and to determine who takes responsibility for the failure.

**Industry responsibility**

When asked about the manufacturer’s degree of responsibility if an implant fails, Dr Maree responded that the industry has clear responsibilities with respect to post-market surveillance. Manufacturers can either merely react to complaints, or be very proactive by using multiple data sources that include registries, literature reviews and case reports to conduct post-market surveillance. The industry also has a responsibility with respect to regulation, to ensure that the lessons of the past are applied to future generations of innovation. Hence, engineers scrutinise results from registries and use them as input to perform root cause analyses of devices failures to improve their understanding of the failure mode and effects. Several companies have set up patient support programmes in cases of device failures, independently of any other programmes and before the root causes have been assessed. The medical device industry thus has a very important role in the
partnership that surrounds a registry. This partnership in turn has a responsibility for enhancing patient care and safety.

**Summary and next steps**

Professor Graves allayed any local concerns by pointing out that in setting up a new orthopaedic device registry, Singapore would join a well-established international community of registries that work increasingly closely together. Any significant infrastructure needed to implement an orthopaedic registry, such as prostheses databases, would be provided free of charge by this network.

He and co-chair Professor Krishnan agreed that the barriers to implementation raised during this discussion have already been faced and overcome by other existing registries. An important task is to reassure surgeons that an orthopaedic registry will offer them considerable benefits and will not be used as a punitive tool. Establishing the purpose of the registry, the sources of funding, and a protocol to follow in the event that any medical device failure is detected, are the other steps to take in order to achieve the HSA’s goal of successfully establishing an orthopaedic medical device registry in Singapore.
Session 2: Cardiovascular device registry

Session objectives

During the second of two sessions that focussed on orthopaedic and cardiovascular medical device registries, respectively, roundtable participants were presented with the academic, industry, and clinical perspectives on cardiovascular medical device registries, to facilitate the final discussions on how to establish these registries in Singapore.

This session’s objectives were as follows:

- To provide perspectives from regulators, academics, industry and healthcare professionals on cardiovascular device registries
- To share information about J-MACS and its harmonisation with the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS)
- To share information about the ACC’s NCDR
- To discuss the role of industry in public-private partnerships for building global medical device epidemiology and surveillance capabilities
- To discuss the benefits to and impact of cardiovascular device registries on healthcare systems, public health and industries.

Regulatory perspective: Medical device post-market surveillance in Japan – harmonising registry data in J-MACS

Dr Madoka Murakami, Unit Chief of the Division of Regulatory Cooperation at the Office of International programs in Japan's PMDA, began by giving a brief overview of medical device regulation in Japan, before describing the Japanese national ventricular assist devices (VAD) registry, J-MACS.
In Japan, medical devices are classified into four classes according to risk, in line with Global Harmonization Task Force (GHTF) guidelines. With regard to pre-market review, the classes are regulated differently, with PMDA approval only required for regulation of devices of Class IIb and above. However, post-market safety vigilance and surveillance is conducted by the PMDA and Japan’s Ministry of Health, Labour and Welfare (MHLW) for all categories of devices. As part of their post-market surveillance systems, Japan carries out re-examination of data from new devices for 3–7 years after launch, because pre-market clinical trial results can be limited when compared to long-term use of a device in the real world.

J-MACS\textsuperscript{11} is a post-market data-collection initiative for VAD in Japan. This prospective, multi-site, observational registry achieves 100% participation rates and is a collaborative effort that involves industry (i.e. manufacturers of VADs), the Japanese government, and academia (six academic societies and one research group). Interaction between the various stakeholders provides a clear structure and framework for the exchange of information.

J-MACS was launched as part of the PMDA’s goal to strengthen and improve safety measures, by constructing a system to gather and evaluate data on the operational status of high-risk implantable VADs. Data quality is assured, with third-party monitoring being carried out.

The registry design of J-MACS is harmonised with that of INTERMACS,\textsuperscript{12} a North American registry established in 2005 for patients who have received mechanical circulatory support devices to treat advanced heart failure. J-MACS therefore lends itself to future data pooling with INTERMACS. Basic data points, including the timing of data collection and the definition of adverse events, are the same as those of INTERMACS, although J-MACS also include unique data points and definitions specific to Japanese requirements. Post-implant follow-up data are collected after 1 week, 1 month, 3 months, 6 months and every 6 months thereafter. Major outcomes after implant insertion, e.g. death, explant, rehospitalisation and adverse events, are entered as they occur, and also as part of the scheduled follow-ups. All data are sent to the J-MACS data centre through the J-MACS web-based data entry system.

\begin{footnotesize}
\begin{itemize}
\item \textsuperscript{11} http://www.pmda.go.jp/english/service/j-macs.html
\item \textsuperscript{12} http://www.uab.edu/intermacs/
\end{itemize}
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Organisationally, J-MACS has three main bodies: a Management Body, a Supporting Body and the Participating Members Body. In addition, there is an Observational Safety Monitoring Board and a Clinical Event Adjudication Committee. J-MACS is strongly associated with the mandated processes of meeting Conditions for Approval and the re-examination of implantable VADs. As a requirement of the Conditions for Approval, manufacturers must work with the relevant academic societies to establish practice criteria for appropriate device use. VAD practice criteria mandate participation in J-MACS and registration of patient data into J-MACS. Regulatory processes involving adverse event reporting are linked to J-MACS.

As of February 2013, 156 patients who have implantable or extracorporeal devices were registered in J-MACS. The PMDA does disclose general information from J-MACS, including statistical reports and adverse events evaluation reports, on its official website. Access to the data centre is limited, but if J-MACS personnel wish to use data for research or publication purposes, these data, with the exception of raw data, will be provided, subject to the appropriate applications being made.

J-MACS was initially designed with a view to sharing data with INTERMACS, but since the International Mechanically Assisted Circulatory Support (IMACS) registry has recently been launched by the International Society for Heart and Lung Transplantation as the global VAD registry, the J-MACS steering committee is now discussing participation in IMACS instead.

**Academic perspective: Key NCDR registries enhance device safety**

The NCDR has eight registries (Figure 3) and represents a $25 million investment per year for the ACC, according to its past president, Professor Ralph Brindis. The initiative came about after the U.S. FDA approached the ACC with concerns about adverse event reporting related to groin closure devices in cardiac catheterisation.\(^\text{13}\) Data from NCDR registries and other stakeholders have been used to generate numerous publications about a range of outcomes, including off-label utilisation, subgroup analyses and other aspects of cardiovascular device performance that cannot be studied in clinical trials. The disadvantages of registries are that they can be episodic, hospital-based and procedural-based, without longitudinal follow up. One strategy to overcome this involved merging

\(^{13}\) Tavris D et al. *J Invasive Cardiol* 2005; 17:644-50
longitudinal data from Medicare payers with clinical data from registries to examine safety and efficacy of drug-eluting stents over a period of 30 months in almost 300,000 patients.  

It is important to maintain long-term sustainability and viability of registries. To this end, registries should be tailored to fit more efficiently into the post-market surveillance environment. One example is the Implantable Cardiac Defibrillator (ICD) Registry, a repository of data on ICD implantation, which was modified to include data on leads to maintain its long-term viability. The ICD Registry captures:

- ICD/CRT-D generators for primary and secondary prevention
- atrial, ventricular, defibrillator, and left-heart lead data at the time of implant, revision, replacement, or abandonment
- paediatric ICD implantation data.

In 2012, nearly 30 papers were published using data from the ICD Registry.

The Transcatheter Valvular Therapy (TVT) Registry was developed to track patient safety and real-world outcomes related to the transcatheter aortic valve replacement (TAVR) procedure, a treatment option for patients whose condition is considered to be inoperable in terms of conventional aortic valve replacement surgery. Through the capture and reporting of patient demographics, procedure details, and facility and physician information, the TVT

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Registry provides insight into clinical practice patterns and patient outcomes. The TVT Registry measures:

- patient demographics, provider and facility characteristics
- history/risk factors, cardiac status and detailed health status
- well-defined indications for the procedure
- pre-, intra- and post-procedure data and adverse event rates
- outcomes after 30 days and 1 year.

The TVT Registry’s Steering Committee includes not only professional societies, but also the U.S. FDA and Medicare. All devices are captured in the TVT registry because this is tied to reimbursement. Other innovative aspects of the registry include the future incorporation of UDIs, short-term risk-adjusted clinical outcomes, long-term outcomes by linkage with Centers for Medicare and Medicaid Services (CMS) claims data, quality of life outcome data, development of a risk prediction algorithm, appropriate use assessment, and the expansion of U.S. FDA label indications based on registry data, which has never been achieved previously.

According to Dr Brindis, the ideal safety monitoring system should be continuously updated, allow an array of statistical analytic options, monitor multiple analyses simultaneously, have a generic structure, and be widely accessible, offering feedback to source sites and alert notifications to the safety analyst.

Using the US National Research Infrastructure, the numerous components of national registries offer untapped opportunities for use in post-market surveillance, including research-ready sites, an existing NCDR data capture system, site recruitment, data standards, customised site training, and the ability to synchronise with additional electronic data capture (EDC).

Clinical registries currently offer the only data sources that include granular clinical data needed for risk-adjustment, medical device-identifying information needed to capture specific exposure, and detailed and relevant clinical outcomes. Registries can be used for methodology development, enabling the study of device learning curves for the safety and
effectiveness of newly introduced devices.\textsuperscript{15} Automated surveillance, as carried out in the Data Extraction and Longitudinal Time Analysis System (DELTA), can fill gaps in current passive reporting approaches by monitoring accruing datasets for low frequency safety signals. The DELTA system imports clinical data in real-time from an electronic database, and generates alerts for potentially unsafe devices or procedures. Alerts must be considered to be hypothesis-generating, and they require additional epidemiologic confirmation, such as pre-specified sensitivity analyses and validation in external data sources. The decision on how and when to communicate the discovery of potential problems with medical devices requires further exploration, to enable rapid escalation of potential high-risk signals. Transparency is required at all levels of the process.

Improvements in today’s registries are still needed because they capture data only for specific devices and conditions, and longitudinal follow-up is limited. The future for device registries will involve the combined use of electronic health records, data abstraction, claims data, safety monitoring systems, UDIs, quality report standards, health information exchanges and standardisation of electronic health record (EHR) platforms. Dr Brindis concluded that registries of the future will also involve societal collaborations between multiple stakeholders: practitioners, health systems, government, industry, health plans, state regulators and accreditors/certifiers.

\textbf{Industry perspective on post-market registries for cardiovascular devices}

The industry perspective on cardiovascular device registries was presented by Ms Roseann White, Senior Director in Global Biometrics at Abbott Vascular, US. In addition to the NCDR registries described above, Ms White listed other large, well-designed academic registries in the US: Duke Databank for Cardiovascular Diseases, Mayo Clinic Cardiac Database, The Massachusetts Cardiac Study and the New York State Cardiac Registries. Examples of ongoing registry collaborations involving industry include the Dual Antiplatelet Therapy (DAPT) Study,\textsuperscript{16} which involves eight manufacturers, Harvard Clinical Research Institute and the U.S. FDA; and the industry’s collaboration with the STS/ACC TVT Registry. The Swedish Coronary Angiography and Angioplasty Registry (SCAAR) has enabled considerable

\textsuperscript{15} Resnic FS et al. \textit{JACC: Cardiovasc Interventions} 2012; 5:82-89
\textsuperscript{16} http://www.daptstudy.org/
advancements in therapy by providing trackability, conformability, and information about device failures and ad hoc techniques.

Medical device manufacturers are strongly in favour of registries because they facilitate post-market surveillance that enables them to improve device efficacy and safety. A common registry design would be ideal, but each registry’s designers are convinced that they collect data optimally, so achieving consensus on registry design can be challenging. For their post-approval studies, which are often single-arm studies comparable to a registry, the industry would ideally prefer to use data from existing registries as part of their post-approval commitment. In Table 6 are shown the goals of post-approval studies that could be addressed using a carefully constructed surveillance study approach. Additional components include a large network, observational surveillance data collection and the use of appropriate statistical methods.

<table>
<thead>
<tr>
<th>Goal</th>
<th>Requirement</th>
</tr>
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<tbody>
<tr>
<td>Broad patient population</td>
<td>Minimal enrolment criteria</td>
</tr>
<tr>
<td>Broad physician population</td>
<td>Large network with multiple provider types</td>
</tr>
<tr>
<td>Real world usage</td>
<td>Observational surveillance</td>
</tr>
<tr>
<td>Long term performance</td>
<td>Patient retention</td>
</tr>
<tr>
<td>Subgroup performance</td>
<td>Baseline variables to describe subgroups</td>
</tr>
<tr>
<td>Adverse event monitoring</td>
<td>Process for signal escalation</td>
</tr>
</tbody>
</table>

The DELTA system’s automated surveillance previously mentioned by Dr Brindis can fill the gaps in current passive reporting models, and has enabled the detection of safety signals by analysing adverse event rates and propensity scores using pooled registry data from several high-volume centres.¹⁷

Ms White reiterated the importance of being able to communicate to the patient community at large the detection of a safety signal, i.e. information about a product that indicates an unexpected risk to patients or users. She described the process of safety signal escalation at the CDRH, which involves four escalation levels. Once the signal is identified, frontline management is alerted. If warranted, the signal is escalated to a network leader, or action is taken by a single office. If required, a working group is then established – the fourth level of escalation. At each stage, the decision is taken as to whether to de-escalate and store the information, to collect more information, or to escalate to the next level.

Ms White concluded that collaboration between regulators, academia and industry is needed to develop registries that are informative and that identify current unmet needs. Statistically valid methods are needed to identify potential safety concerns, and a process for escalating and acting on potential safety concerns must be put in place.

**Cardiologist's perspective on registries for cardiovascular devices**

Associate Professor Lim Soo Teik, Head of the Department of Cardiology at the National Heart Centre in Singapore, presented an overview of implantable cardiovascular devices used in Singapore (Table 7).

<table>
<thead>
<tr>
<th>Indication</th>
<th>Device</th>
</tr>
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<tbody>
<tr>
<td>Coronary artery disease</td>
<td>Stent</td>
</tr>
<tr>
<td>Cardiac rhythm management</td>
<td>Pacemakers and leads</td>
</tr>
<tr>
<td></td>
<td>Defibrillators and leads</td>
</tr>
<tr>
<td></td>
<td>CRT / CRT-D and leads</td>
</tr>
<tr>
<td>Congenital heart defect</td>
<td>Closure devices</td>
</tr>
<tr>
<td>Valvular disease</td>
<td>Prosthetic valves</td>
</tr>
<tr>
<td></td>
<td>• Surgical</td>
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<td></td>
<td>• TAVI</td>
</tr>
</tbody>
</table>

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According to Singapore’s Health Products (Medical Devices) Regulations 2012, qualified practitioners are required to maintain proper records of implantable medical devices, including:

- name, address and national registration identity card number (if any) of the recipients
- date of the implantation
- name, description of the implantable medical device
- lot or batch number of the implantable medical device.

As pointed out by Professor Lim, a national cardiovascular-related device registry offers the potential to collect data on a lifelong basis, independently of vendors, that will in turn enable efficient traceability, improved clinical management and the identification of safety signals.

The Singapore Cardiac Data Bank (SCDB) was established in 1999. Its aim is to maintain a registry of cardiovascular diseases and relevant procedures performed. The scope of this database includes adult coronary angiography and PCI, adult cardiac surgeries, heart failure, ICD and pacemaker implantations, and electrophysiology study and ablation procedures. The data entry form for pacemakers, leads and pulse generators includes fields for model and serial numbers of the implantable devices, so that in theory, it should be possible to trace patients who have received devices of this nature if a safety signal is identified.

With regard to registry participation, at present, Singapore’s clinicians’ main priority is to generate the electronic medical reports (EMR) to facilitate their patients’ subsequent treatment and healthcare. Providing information for the SCDB is perceived as demanding additional work. It will therefore be important, when establishing a national device registry, to
ensure that the process is designed to make data collection simpler and more complete, for example by linking the SCDB to the EMR. At present, only public institutions contribute to the SCDB, and for the registry to be truly national, Professor Lim believes that all centres (including the private sector) should participate.

At present, the SCDB is funded by the National Heart Centre, but the Ministry of Health may be another funding option. Further issues to be considered when designing a national cardiovascular registry for Singapore include the standardisation of terms and definitions in line with the most recent Academic Research Consortium (ARC) guidelines, the use of UDI for implantable devices, and extended follow-up. Collaboration will be necessary at national (HSA, academia and industry) and international levels (involving IMACS, NCDR, and the Asia Pacific Evaluation of Cardiovascular Therapies Collaboration [ASPECT]). Professor Lim concluded that discussions with the HSA on how to adapt the SCDB to form a national registry of cardiovascular-related medical devices in Singapore have already begun.

**Roundtable discussion: Registries for cardiovascular devices**

Co-chaired by Professor Krucoff and Associate Professor Lim Chong Hee, Chairman of the Chapter of Cardiothoracic Surgeons at the National Heart Centre in Singapore, the purpose of this discussion session was to determine the steps needed to establish a national cardiac device registry in Singapore, taking into account the information shared during the session presentations. The panellists are listed on page 7 of this report.

Professor Krucoff pointed out that, whereas there are obvious similarities between registries across medical device fields, issues that are specific to individual cardiovascular devices must also be taken into account. One aspect in which cardiovascular devices differ from orthopaedic devices is that the function of some cardiovascular devices is dependent on drugs (e.g. anticoagulant drugs for heart valves and dual anti-platelet therapies for drug-eluting stents), or that drugs may affect the same clinical endpoints as devices (e.g. beta-blockers and statins in the case of stents). Monitoring patients’ compliance with their drug regimens is difficult, even in the US, although in the US claims data can be mined because patients get their prescriptions filled. How to evaluate concomitant medications and compliance issues using registries is one unique aspect of the cardiovascular post-market surveillance field.
The following points were raised and debated.

**Optimising registry ability to detect rare safety events: national vs. global**

A large number of well-developed cardiovascular device-related registries already exist around the world. However, the more fragmented the registry environment, the more difficult it can be to detect rare events with any statistical certainty. An increasingly important challenge is how to optimise the signal-to-noise ratio – creating more registries may increase the possibility of injecting even more ‘noise’ into the system, which might obscure weak early signals. The industry may at times even be averse to the proliferation of individual registries, because it can be difficult to extract information and bridge differences in methodology or definitions between different registries to try to obtain a coherent overview. Hence, the industry often favours multi-national collaboration between registries.

In contrast, Professor Graves felt that individuality amongst registries can be beneficial, because it enables innovation and allows each registry to address the local needs for which it was originally designed. Smaller registry efforts require smaller budgets. However, because of its small population, even a national registry in Singapore may be unlikely to detect rare events, and collaboration with stakeholders or registries at an international level would increase the chances of rare signal detection. Another option would be to pool or share individual data from national registries between countries. However, numerous differences of opinion exist as to which data should be collected, from whom, for which devices and for how long, which in turn creates challenges to designing international registries.

**Data pooling and sharing**

An important consideration with respect to globalisation of registries is the ability to facilitate data pooling without full data sharing because of stakeholders’ resistance to loss of control of their data as it may be applied toward the objectives of other stakeholders. Barriers to data pooling and sharing include concerns about compliance with data privacy legislation between different jurisdictions, differences between indications for different devices between
countries and regions, differences in registry design, and the desire to protect proprietary data that confer a competitive advantage.

Several suggestions were made to overcome these barriers. One was to learn from Europe’s medical device directives in the 1980s, the spirit of which was that every country had to incorporate a minimum level of directives into their national legislation, but were then also free to incorporate additional requirements of their choice. In other words, all registries should capture a minimum set of data that can be pooled or shared. For example, Singapore could set up an advanced national registry that also participates in an international registry at the level of a specified minimum, extractable, common set of data.

Ms White pointed out that Bayesian statistics allows an alternative to data pooling – exchangeability, which means that information of exactly the same type need not be collected by all registries. These statistical methods enable a signal to be detected, even if different data types are compared, as long as they are from the same population and concern the same device. In Australia, the ability of non-uniform registries to undertake uniform analysis is being developed, even if not all the registries have collected the entire data set. The ACC has been working on harmonisation and data extraction tools that have the ability to extract information from an electronic health record. The trend is therefore towards techniques that enable registries to pool or exchange certain data, without sacrificing proprietary information or control of data within their specific jurisdictions per se.

**Data quality and standardisation**

The development of infrastructure to enable data pooling (or exchangeability) is critical. In a registry environment where registry and data harmonisation is being sought, establishing standards for data and IT infrastructure is key. According to Ms White, the ideal system would involve being able to extract information from electronic health records. To enable this, a minimum set of definitions should be standardised and included, so that they can be extracted and pooled or shared in registries.

Registry data quality is also a critical determinant of the potential value of registry implementations. Built-in data quality reports are important to ensure comprehensiveness.
and accuracy when populating registry fields. External auditing (which can be expensive) is common in the US, and many of the hospitals that participate in the NCDR also have self-auditing processes in place. Metrics for the missingness of data and strategies to correct for missing data in analyses intended to detect safety signals or otherwise evaluate device performance are informative. With the increase in public reporting, registries become accountable, which is another driver for improving quality. Hence, public reporting adds additional value in terms of post-market surveillance.

**Engaging physicians**

To add physician value, registries should yield quality, benchmarked data in a timely fashion. Physicians will see great value in the ability to monitor patient outcomes and subgroups of patients, particularly in the context of off-label use. Data from registries can also be used to aid education and maintenance of certification. In the US, the idea of appropriate use criteria is becoming very important (i.e. carrying out the correct implantation procedure for the right patient), and requirements for accountability means that clinicians must increasingly be able to justify their methods and outcomes. Registries offer a method of collecting data to demonstrate that a clinician is acting appropriately – another benefit of the increasing trend towards transparency and public reporting.

To increase physicians’ involvement, it is important that they understand that registries are intended as a benefit, and not as a punitive tool. Similarly, the perceived value for physicians must be greater than the perceived burden to the clinical workflow if physician enthusiasm is to be successfully garnered.

**UDIs and traceability**

Significant work has been done to promote international harmonisation in the area of UDIs; first, by the GHTF; and then, by the International Medical Device Regulators Forum. A remaining concern pointed out by Mr Michael Gropp, Vice President of Global Regulatory Strategy at Medtronic Inc., involves the markings that appear on the medical device itself. Much less effort has gone into designing the systems by which those markings and the
information that they convey will be captured as the product moves through the distribution and use channel to the individual patient. The potential value of UDI for traceability has been extensively discussed, but Mr Gropp felt that its full potential will not be achieved if there is no effective, robust, widely disseminated system of capturing those data at the point of device implantation. Much more must be done regarding the downstream capture and use of those data.

He added that, for some devices and in some interventions, systems that capture data and transmit them in a secure fashion to a central database over the life of the product in the patient could be built into the device itself.

**Practical suggestions**

Making the registry as simple as possible has been found to be a good recipe for success.

Ms White suggested that other registries should be examined to determine the most useful common data fields that should be included in Singapore’s national cardiovascular device registry. This will enable sharing with other individual or international registries. Additional data fields relevant to Singapore’s population and requirements can then be added.

At present, data are only collected in the SCDB registry for one year post implantation – this period should be increased, which will in turn require additional funding.

Professor Krucoff recommended using procedurally oriented data capture as a manageable first step, which will enable analysis of hospitalisation and readmission rates. Electronic health records that include a form of patient identifier offer a potential mechanism to detect readmission rates. However, determining the long-term outcomes of these procedures, and the ability to follow patients over the longer term, will be more complex.

Dr Brindis explained a process whereby in the US, clinical data obtained at the time of stent implantation can be merged in a registry with administrative data obtained from a hospital
system. This should provide valuable information related to readmission rates, death indices, causes of readmission, and the need for revascularisation. In this way, low-frequency safety events can be sought in a cost-effective manner.
Session 3: Roundtable discussion on establishing national medical device registries

Establishing registry goals and priorities

The discussion panellists are listed on page 7 and 8 of this report. Session co-chair Associate Professor Lee Chien Earn, Chief Executive Officer of Changi General Hospital, Singapore, reiterated that a registry can have many purposes (e.g. track and trace, signal detection, outcome monitoring or clinical data repository) and for each of these, the process of setting it up, the benefits, and the required costs will differ. It is therefore vital to reach consensus from the outset on the goals and priorities of the registry so that resources can be optimally deployed.

Associate Professor Chan Cheng Leng, Deputy Group Director of the HPRG at the HSA, said that from the regulatory perspective, Singapore’s registries must be multi-purpose. The ability to track and trace is very important, and one of the simplest ways to achieve this would be to link the registry with claims data. Establishing infrastructure that would enable the full use of UDIs to be leveraged will also be vital.

In order to most effectively identify safety signals and the frequency with which they occur in a particular population, it is vital to prioritise which categories of devices and procedures should be included in a registry. ICDs, pacemakers, heart valves, stents, and joint replacements are the subjects of numerous registries around the world. However, systematic data gathering might reveal other devices or processes that might reduce morbidity and mortality to a greater extent if they were the subject of registries. For example, according to the UK’s Department of Health Adverse Event Reporting System, the most frequently reported category of incidents involves hospital infusion pumps, which were not discussed at this meeting, and which are not generally considered for registry inclusion. Demonstrable public health benefits in return for the resources expended is an important goal for a registry.

The comparatively small population of Singapore could pose a barrier to effective safety signal detection unless data are shared or pooled with other countries and registries. Singapore must therefore determine in which areas it can rely on data gathered by other regulators and databases before interpreting it within the context of its own healthcare environment and population, and in which cases these data should be gathered from its own...
population, in order to most effectively identify safety signals. Characteristics particularly unique to Singapore with regard to the nature of the population and the practice of medicine must therefore be considered during the first planning stages.

**Factors required for track and trace and safety signal detection**

There was much debate around the feasibility of using registries to detect safety signals and for track and trace purposes in Singapore. Methods to achieve these goals were also discussed.

Mr Rainer Voelksen, Vice President of International Regulatory Affairs at Edwards Lifesciences, pointed out that Switzerland has a similar population size to Singapore’s, and that tracking and tracing in that country does not pose a problem because of the existing system of industry obligations. Their system enabled the authorities to recall hip prostheses after 10–15 notifications among 150 implants in Switzerland.

In Changi General Hospital, an e-register of all the devices that are implanted in the operating theatres will soon be implemented. This comprises an online system whereby patients and devices are barcoded, so that by matching the two barcodes, patients and devices can be linked and tracked, and the data easily accessed if required. Professor Low Cheng Ooi, Chief Medical Information Officer at Singapore’s Ministry of Health, suggested that the HSA should base their registry design on an existing hospital-based system such as this one, and then build incrementally on this. Extracting data from hospital registration databases on whether patients returned for revision surgery can form the basis of track and trace at the institution level, but this would be hampered if patients returned to different centres for their revisions. Expanding the SCDB to cover the private sector was another suggestion, but this would require additional funding for data capture. All Singapore residents have National Registration Identity Card (NRIC) numbers, and Medisave claims can be linked to the implants used in individual patients – these factors should in theory facilitate device tracking and signal detection. Even data on batch and lot numbers are captured in most hospitals, although often in a form that can only be accessed manually.
Associate Professor Koh Tian Hai, Medical Director, Medical Director's Office at the National Heart Centre pointed out that Singapore’s National Disease Registries, which contain data on myocardial infarctions, strokes, renal failure and cancers provide an excellent source of data, especially in the cardiac field, particularly if they could be linked to the Ministry’s data on births and deaths, to obtain information about mortality.

Hence, it is clear that the required information exists in Singapore, but often in different databases or in formats that hamper accessibility and utility. As previously mentioned, it is difficult to link data stored in different fields that are defined in different ways between databases. The ultimate goal should therefore be an integrated system that captures all data at the point of implant. UDI could play a key role, although much of the infrastructure still remains to be developed. A primary task will therefore be to convert the data needed for track and trace purposes into an electronic format that is consistent and potentially accessible to other registries or databases.

Dr Graves summarised the basic requirements of a device tracking system or registry. The device must be identifiable by catalogue number and lot number, and linked to a patient. The system must show whether the patient is still alive, whether the device still in place or has been removed, and whether the patient has been re-admitted for revision surgery. These pieces of information will form the basis of a useful registry that allows assessment of outcomes and detection of safety signals.

Associate Professor Lim Soo Teik suggested that the HSA could consider a nationwide catheterisation laboratory and operating theatre inventory system, whereby the barcodes and radio frequency identification (RFID) could be scanned to capture the model and serial number of the devices, to facilitate comprehensive data capture.

**Overcoming barriers to data pooling to facilitate safety signal detection**

Professor Krishnan acknowledged that even in Singapore, people are resistant to centralised data storage and sharing because they fear loss of control, but data pooling is vital if rare safety events are to be detected because the process is dependent on large sample sizes. According to Professor Krucoff, individual databases are underpowered to detect rare
catastrophic events such as, for example, a stent thrombosis. He added that it is also important to consider not only the number of procedures that are carried out per year in Singapore, but also the likelihood of an associated adverse event – for example, in transvalvular aortic valve implantation, the density of adverse events is rather higher.

Giving the industry perspective, Dr Maree stated that, although industry concerns about the proprietary nature of their data have been overstated at times, constraints around innovation must be recognised. Device manufacturers would like the reassurance that the data requested will be used effectively, and specifically to enhance patient care and treatment standards.

To address the issue of widespread reluctance to share registry data, Dr Krishnan described the Federated Data System that has worked well in the US and is currently used mainly in the medical fields of oncology and imaging. It enables pooling of data in an anonymous manner using standardised software, and offers a useful approach.

In the US, the NCDR was initiated by professional societies such as the ACC. In Sweden, registry is mandated and supported by the government and covers 100% of catheterisation laboratories. A strong leadership approach will be required to achieve consensus on the processes needed and responsibilities to be shouldered in Singapore.

A suggestion was made for the ASEAN community, led by Singapore, to pool their efforts in a Federation-type system, and to analyse the data by race to detect safety signals.

**Longer-term goals: actions following safety signal detection**

It will be important to set up procedures to facilitate not only safety signal detection, but also signal escalation and the ability to contact the affected patients efficiently. An email address and mobile phone number may be more useful than home addresses in tracing patients in today’s world.
Spontaneous adverse event reporting systems still have an important role to play in detecting rare events. The FDA and Europe use similar forms for this process, which can provide a useful starting point for Singapore.

Mr Gropp pointed out that the industry has a very high regard for the privacy of the physician-patient relationship in handling field safety corrective action, and that industry is reluctant to be seen to intervene in that relationship. Hence, the industry perspective is that, in the event of a safety signal, they would provide as much information as they reasonably can, given the facts available to them at the time, to the physicians, who must then determine how best to manage that information for each particular patient. Dr Cook agreed that it should be the health professional, preferably the implanting or operating physician, who communicates that information to their patient because of the many contextual issues that need to be taken into account. In Australia, if the health professional is no longer available, the TGA works with state and territory health departments and hospitals to try and reach affected patients, depending on the type of implant. The TGA also disseminates messaging via the press, as does the U.S. FDA and the European Medicines Agency (EMEA), to alert people to a particular recall or problem, and encourages them to visit their own physician to follow up on that information.

Professor Krucoff pointed out that traditional signal escalation processes have not always taken into account the differences that exist between devices and drugs. For example, the device may be malfunctioning, or the operator may have created a situation where the device will malfunction. The role of each stakeholder in the degree to which that signal should be escalated must be determined.

Dr Maree emphasised that, rather than only making provision for who is responsible if something goes wrong, it is more important to develop a process for working together to get things right. Stakeholders must develop processes to aid understanding of the root causes early on if a signal is detected, and to effect positive change that goes beyond compliance issues. He added that in the UK, the process involves leveraging additional multiple interpretive datasets, in addition to high-quality registry, to ensure that patient-centred decisions are the priority.
Existing registry approaches

In the US, numerous cardiology-related registries exist, and these are focused mainly on implantable devices. There is strong interest in developing a peripheral intervention registry to go with peripheral devices.

INTERMACS provide another example of a useful registry design.

The UK has numerous registries, but few are device-specific. Cardiology registry activity in the UK is fairly rudimentary at present, according to Mr Wilkinson, and consists mainly of information collected by industry stakeholders. The UK has two approaches to device registry. The short-term approach involves setting up numerous registries to target areas considered to be a risk for safety signal detection. The longer-term approach involves the use of UDI for all devices, which are collected at the point of insertion. Overlaying this is the UK’s Clinical Practice Research Data link, which is currently connected to approximately 7 million GP records (the target is to achieve 25 million records). Once these data are combined over the longer term, it will provide the opportunity for numerous observational studies to be carried out, which could even supplant the registries set up for the short-term. The ultimate goal is an integrated system.

Mr Verstappen suggested establishing national registries in Singapore and then expanding the initiative to include pooled data from other countries, based on approaches taken by Eucomed and the GHTF. Initially the differences that exist between countries may prove challenging, but if the project seems attractive enough, eventually stakeholders will become aligned.

Achieving buy-in and compliance

The success of a registry is determined by the various stakeholders and the manner in which they collaborate to set up the registry. The benefits must be apparent to each stakeholder,
whether this takes the form of faster reimbursement for the physician, or product information that will be helpful to industry or regulators.

Professor Krucoff suggested that Singapore should widely publicise the establishment of these registries as the creation of a national health care “treasure." The clinical community and governmental agencies should be seen to work together, with support from industry, to contribute to the greater public good. A positive awareness campaign should be instituted to reassure physicians and patients that a national registry is not a tool to be used to attach blame or collect private data, but rather a system that will provide numerous long-terms benefits to the hospital, the physician, the patient and industry to make better devices. Registry users and the public must be reassured that when a registry does detect a safety signal, this will produce a positive outcome.

Proposals to obtain physician buy-in for registries included: (i) emphasising the registry’s role in clinical quality improvement by publicising monthly data on device recalls; (ii) linking Medisave payments by private sector patients to the submission of data to the device registry; (iii) convincing hospitals that registries will facilitate tracking and tracing and is preferable to manually searching records; and (iv) legislation to ensure that data will be collected from the private sector.

These registries would provide added value if the initiative could include a government-issued or other national solution to ensure UDI capture at every bedside. Mr Gropp pointed out that the prominence of government initiatives is well established in Singapore. Being a small, unitary state with a small number of hospitals, Singapore could provide an interesting test case at an international level for the implementation of the infrastructure required to gather UDI data at the point of use.

With regard to funding these registries, Associate Professor Lee Chien Earn suggested that the Ministry of Health might be willing to fund a track and trace component because of its relevance to the Ministry, but that funding from other stakeholders, possibly industry or device users, should be sought for to achieve additional registry goals.
Dr Maree stated that manufacturers derive great value from well-designed and -executed registries, in terms of influencing innovation in research and development, improving patient care, and elevating treatment practices and treatment standards. He felt that industry would be willing to contribute to funding a registry if invited to be involved in its design and set-up, but would be less likely to provide funds for a registry that is drawn up in a vacuum that does not involve the industry.
Taking the first steps

Professor Ralph Brindis outlined some steps that could be taken to initiate the process of setting up national medical device registries in Singapore.

Firstly, the stakeholders (physicians, government regulators, consumers, and representatives of relevant health systems, health plans and industry) must be identified so that they can work together to determine a mission statement, registry goals and a financial model. Examples of funding structures include a hospital subscription model; an industry-funded model; a payer-funded model; government funding; or a combination of all these mechanisms.

A steering committee should then be established to enable the stakeholders to work together to achieve these tasks. A scientific committee will also be required to determine the data elements that must be collected, and whether the registry will leverage existing designs from around the world, be individualised to Singapore’s needs, or include elements from both options. An analytical centre and procedures will be necessary, and decisions must be made about responsibilities and outsourcing requirements. Eventually, a research and publications committee can be set up to mine and disseminate findings from the registry.

Professor Krucoff concluded that these discussions had provided useful guidance on achievable first steps that can be taken towards achieving the final goal of setting up medical device registries in Singapore. In his concluding remarks, Dr Krishnan emphasised that the momentum generated by this initial meeting should be maintained by on-going exchanges and directed actions.
Summary and call to action

Associate Professor Lee Chien Earn summarised the day’s proceedings and outlined the next steps to be taken.

1. The first step will be to achieve consensus on the registries’ desired outcomes with regard to:
   - track-and-traceability of devices
   - signal detection
   - clinical outcomes
   - research.
   
   These objectives may differ for medical devices used in different fields.

2. Operational considerations in the development of registries include:
   - clinician buy-in
   - linking with other databases
   - pooling of data at institutional, national and potentially at the ASEAN level
   - governance regarding data integrity, quality and security
   - long-term follow-up
   - sustainable funding
   - scalability.

3. Processes must be established to link data with actions in terms of:
   - response to early signals
   - signal escalation
   - recall processes
   - stakeholder responsibility.

Professor Lee emphasised that many opportunities are available to the HSA in the form of the design, experience and expertise used in developing and implementing existing local and international registries and databases, and other relevant initiatives such as UDI.
4. Collaboration at a local, regional and global level across all the various stakeholders will be a key factor for success.

In his final call to action, Dr Lee laid out two key points.

- Between this meeting and the next, to be scheduled approximately a year from this one, the HSA must examine Singapore's existing capabilities and on-going initiatives that could be leveraged to develop the appropriate registries, to prevent duplication of effort and to help determine the resources required.

- The second step is to identify the stakeholders that are willing to collaborate in taking the steps towards setting up a pilot medical device registry in Singapore, and who understand the operational and logistical challenges.

Dr Raymond Chua concluded that this roundtable meeting had provided the HSA with the catalyst and recommendations it needs to facilitate a collaborative effort with local and global stakeholders to execute registry implementation that can not only achieve medical device traceability in Singapore, but will also improve health outcomes for patients, nationally and globally.
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