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1. Executive Summary

The Medical Technology Association of Australia (MTAA) welcomes the opportunity to respond to the TGA consultation on Draft clinical evidence guidelines – Medical devices which was opened on March 15, 2016. We would like to commend the TGA for drafting this comprehensive and detailed guideline which provides clarity and predictability for medical technology manufacturers.

In Section 1 Introduction of the TGA draft guidelines it is stated: “All medical devices supplied in Australia must have clinical evidence sufficient to demonstrate an appropriate level of safety and performance when used for the intended purpose(s). […] Clinical evidence is required not only when a medical device is first included on the register [Australian Register of Therapeutic Goods or ARTG] but for the entire period it remains on the register. The TGA may request and review this clinical evidence at any time. Clinical evidence is frequently requested when there is an application for inclusion of a device on the ARTG, a review of conformity assessment procedures or when a safety issue with a medical device has been identified.”

Clinical assessors expect to see clinical evidence that provides “a current and accurate picture of the state of scientific knowledge in relation to the treatment modality in general to which a device relates, and then with respect to the particular device specifically” (TGA, 2016). The clinical evidence must demonstrate that the medical device has an acceptable risk or safety profile, that it performs as intended and that all identified undesirable effects and hazards are outweighed by the benefits. The detail and extent of the clinical evidence will depend on the classification of the device, its nature or design and the purpose(s) for which it is intended. This clinical evidence should be updated and systematically reviewed periodically as new information based on post-market surveillance activities and product experience becomes available.

The MTAA is committed to ensure that the benefits of modern, innovative and reliable medical technology are delivered effectively to provide better health outcomes to the Australian community. The MTAA has been advocating for alignment with the European Union (EU) regulatory requirements, as well as with international best practices and regulatory harmonisation. In preparing this submission the MTAA has taken into consideration regulatory requirements and practices for clinical evidence defined in:

- EU MEDDEV guidance 2.7.1/ Rev. 3 Clinical evaluation: A guide for manufacturers and notified bodies (European Commission, 2009)

The MTAA position on requirements for clinical evidence demonstrating the safety of Implantable Medical Devices (IMDs) in the Magnetic Resonance (MR) environment (Section 6, pages 91 to 105 of the TGA consultation draft document) is submitted in a separate position paper which is only referenced in this submission.
2. MTAA recommendations

Recommendation 1
The Introduction section of the TGA draft guidelines makes it clear that this guidance applies to IVDs as well. However, the terminology used throughout the document is specific to non-IVD medical devices. The Key definitions and concepts section of this document, consistent with GHTF document Clinical Evidence – Key Definitions and Concepts, defines terms such as clinical evaluation and clinical data only in the context of non-IVD medical devices. In practice, such terms are not used for in vitro diagnostic devices, where terms such as performance evaluation and performance data are employed. IVD-specific terminology is absent from this document and should be introduced.

Recommendation 2
The specific involvement of clinical experts responsible for the literature report should be that of “authorised signatory”, and not necessary as “author” (Section 3, Clinical evidence, page 19).

Recommendation 3
Additional clarifications should be provided in the guidance for the supporting documents required with the clinical evidence (Section 4, Supporting documents, page 27).

Recommendation 4
Terminology used in this guidance document should be consistent with the terminology used in the Review of Medicines and Medical Devices Regulation – Stage One Report of March 2015. For example, the term ‘comparable’ should be used instead of ‘recognised’ to refer to markets under the jurisdiction of regulatory authorities that are comparable to the TGA (Section 5, Substantial equivalence, Step 1, page 36).

Recommendation 5
Randomised controlled clinical trials, while representing the gold standard for medicines, are in most cases unsuitable for medical devices. Hence they should not be considered as “preferred” for medical devices (Section 6, Clinical investigation(s), pages 42, 51, 73 and 82).

Recommendation 6
Clinical quality registries, where available, can provide a high level of ongoing safety monitoring during the post-market phase. The TGA could use the data from such registries to ensure adverse event reporting aligns with the actual experience. Until then though, industry must rely on available information provided via spontaneous reporting. (Section 6, Post-market data, pages 44, 52, 63, 75 and 83).

Recommendation 7
Equivalence for MR safety should be defined using aspects that are relevant to MR safety only, not all aspects considered when determining substantial equivalence in general (Section 6, pages 92 and 95). AIMDs that are equivalent from a MR safety point of view with existing predicates already determined to be ‘MR safe’ should not require direct clinical evidence if their MR safety status can be determined using simulation and modelling testing according to ISO/TS 10974:2012 Assessment of the safety of magnetic resonance imaging for patients with an active implantable medical device. The rationale for this position is further elaborated in the MTAA Joint Industry Working Group (JWG) Position Paper Evidence Requirements for Magnetic Resonance Imaging (MRI) Labelling of Active Implantable Medical Devices (AIMDs).
**Recommendation 8**

Manufacturers of Implantable Medical Devices (IMDs) should be able to decide whether to supply a patient card or whether to use other means for providing essential product information, including MRI safety status. The chosen medium should be appropriate for the type of implant in accordance with the relevant Essential Principles. (Section 6 Requirements for specific high risk devices, sub-section “Demonstrating the safety of IMDs in the MR environment”, page 105).

**Recommendation 9**

The draft guidance requirement regarding image artefact information should be replaced with a requirement to include a general cautionary statement in the IFU to indicate that image artefact and distortion can result for the device and that these factors should be considered when interpreting the MRI images. (Section 6 Requirements for specific high risk devices, sub-section “Demonstrating the safety of IMDs in the MR environment”, page 104, 6th bullet point).

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**3. Detailed rationale**

**Section 1 Introduction**

The MTAA agrees with the content and has no further comments to Section 1 Introduction of the consultation document.

**Section 2 Legislative basis**

We suggest adding a clarification at the end of the second sentence in the second paragraph under the heading Compliance with Essential Principles (page 9) to reflect the principle that compliance with the EPs is related to the intended use and risk profile associated with the device (proposed changes are shown in underlined text): “The principles do not set out categorically how manufacturers should comply with these but leave some room for flexibility according to device intended use and risk profile”.

Under the heading Principle One: Use not to compromise health and safety (page 10) the wording used applies to non-IVD medical devices only, e.g.: “what sort of treatment is administered”. The MTAA recommends that explanations relevant to IVDs are also included.

Under the heading Standards (page 12), the guidelines should mention which standards are applicable to both IVD and non-IVD medical devices, and which standards apply only to non-IVD medical devices.

The wording of the second paragraph under the heading ISO 14155:2011 Good clinical practice (page 13) leaves the impression that using clinical evidence from literature is not in compliance with ISO 14155. We recommended updating with the proposed wording for clarification. Also, the second sentence in this paragraph should be amended as follows (proposed change is shown in underlined text): “Any clinical research not undertaken in compliance with this standard (such as using data from trials which are not compliant with ISO 14155) would be of less evidentiary weight, all other considerations notwithstanding, as
the principle aim of this standard is to ensure protection of study subjects and the credibility of the data gathered."

### Section 3 Clinical evidence

The **Key definitions and concepts** (page 15) should include definitions and concepts relevant to IVDs.

The requirement on page 19 under the heading **Literature report** states: “A report must be provided, written by a competent clinical expert, containing a critical appraisal of this compilation, […]”. This requirement implies that the clinical expert must actually write (i.e., author from scratch) the literature report. In reality, clinical experts may write the report themselves or may review a draft provided by a clinical writer and make changes as needed. Therefore we suggest amending the text of this requirement as follows (proposed changes are shown in underlined text): “A report must be provided, **signed and dated** by a competent clinical expert, containing a critical appraisal of this compilation, [...]”.

The terms “adverse event rate” and “device complaint rate” on page 19 under the heading **Post-market data** need further definition so that complaints “as reported” can be differentiated from complaints “as confirmed on analysis”.

### Section 4 Clinical evaluation report and supporting documents

In sub-section 2. **Intended purpose/ indications and claims** (page 22) it is stated that information on magnetic resonance (MR) status of the device should be included in the product accompanying documentation. Since this requirement is only relevant to Implantable Medical Devices (IMDs) we suggest to add the wording “as applicable” at the end of the sentence.

Terminology and examples used to describe the authorised signatory of a clinical evaluation report (CER) should include terminology and examples relevant to IVDs (pages 27 and 107). For example, the expert signing the CER for an IVD can be a pathologist, medical scientist or university professor and not necessary a "clinician" (medical doctor).

Under the heading **Supporting documents** (page 27) the guidelines list the supporting documentation that should be provided for pre- and post-market reviews in addition to the clinical evaluation report (CER). We would like to suggest the following changes to this list (proposed changes are shown in underlined text):

- Preclinical data (if relevant)
- Full clinical investigation reports (if necessary)
- Literature search and selection strategy
- Full text articles from literature review (if necessary)
- Full technical and physical specifications of the device (i.e., design outputs)
- Risk analysis and management documents
- Post-market data

Rationale for suggested changes:
B. Full clinical investigation reports should only be required if necessary, i.e. for novel technologies or significant changes to the indications for use of an already approved device. Most medical devices consist of incremental design and/or manufacturing improvements to existing, marketed devices. Hence safety and effectiveness can be demonstrated by bench testing and clinical data obtained from predicate/similar devices as well as post-market data.

D. Full text articles from literature review should only be required if necessary as this could potentially include thousands of pages and the referenced documents are readily available online. Me-too devices would typically not require anything more than a literature review and an updated post-market data summary.

E. Full technical and physical specifications of the device must be clarified as being the design outputs. The term “specification” is often used interchangeably to mean “design requirements specifications” which are design inputs and “manufacturing specifications” which are design outputs. Required here are design outputs as defined in ISO 13485 Section 7.3.4.

Also, we seek clarification with regards to the level of detail expected by the TGA for the above mentioned documentation. For example, “full technical and physical specification” may consist of hundreds or even thousands of documents. A summary with enough information would be more appropriate for a regulatory submission.

Section 5 Demonstrating substantial equivalence

Under the heading Substantial equivalence, in Step 1 Identification of a predicate or similar marketed device, second paragraph (page 36), we suggest to replace “recognised international market” with “market under the jurisdiction of a ‘comparable’ regulatory authority” to be consistent with the terminology used in the Review of Medicines and Medical Devices Regulation – Stage One Report of March 2015. Alternatively, please specify what a “recognised international market” is.

Section 6 Requirements for specific high risk devices

This section does not include any examples relevant to IVDs; it should also include examples specific to IVDs.

Under the heading Clinical investigation(s) (pages 42, 51, 73 and 82) it is stated: “The preferred design is a randomised controlled clinical trial […]”. Randomised controlled clinical trials are indeed the gold standard for medicines but for medical devices such trials are, in most cases, unrealistic. The lifespan of a device is much shorter compared to a medicine, and the majority of regulatory submissions are for incremental improvements to existing marketed medical devices. Therefore large, long running, randomised clinical trials would be excessive for medical devices.

For novel devices we would like to refer to processes adopted by the U.S. FDA, whereby the FDA accepts clinical data from small-size clinical trials for the “pre-approval” stage and works together with manufacturers to set up registries for the purpose of ongoing data collection. Such small trials, while they don’t meet the criteria for randomised controlled clinical trials, provide enough assurance of safety and effectiveness to allow patient access
to novel medical technologies. Clinical quality registries, where available, can provide a high level of ongoing safety monitoring during the post-market phase.

Under the heading **Post-market data** (pages 44, 52, 63, 75 and 83) it is stated: “For reports of adverse events and device failures to be useful clinical evidence, the manufacturer must make a positive, concerted effort to collect the reports and to encourage users to report incidents. Experience shows that merely relying on spontaneous reports leads to an underestimation of the incidence of devices failures and adverse events.” It appears that an assumption is being made that the adverse events reports provided by the industry are underestimates, however the majority of medical device suppliers have robust adverse event reporting processes in place where global incidence rates are regularly monitored and corrective actions implemented as necessary. Clinical quality registries, where available, can provide a high level of ongoing safety monitoring during the post-market phase. The TGA could use the data from such registries to ensure adverse event reporting aligns with the actual experience. Until then though, industry must rely on available information provided via spontaneous reporting.

In section **Demonstrating safety of IMDs in the Magnetic Resonance (MR) environment**, under the heading **Summary recommendations** it is stated: “For submissions reliant on predicate, or similar marketed device data, sponsors are advised to submit all relevant documents with a supporting clinical justification that establishes substantial equivalence between a device and the nominated predicate(s) or similar marketed device(s)” (sixth bullet point, page 92).

Further on, under the heading **Substantial equivalence** it is stated: “Data for a predicate device (for example, earlier version of the device made by the same manufacturer) may satisfy the requirements for evidence provided the devices have been demonstrated to be substantially equivalent in relation to their intended use, design, technical modifications, engineering, materials and biocompatibility” (second paragraph, page 95).

We argue that at least some criteria mentioned above, such as biocompatibility, are not relevant to MR safety. We suggest to reword relevant paragraphs to define when IMDs are considered substantially equivalent from an MR safety point of view. In defining MR safety equivalence we recommend to use the following criteria:

- Same intended use
- Same principle of operation and technology
- Meeting the minimum requirements for the potential hazards identified in Table 4 (page 99), expressed in maximum admissible limits or minimum admissible limits, as applicable, using simulation and modelling testing defined in ISO/TS 10974 Technical Specification, ASTM F2052 and ASTM F2213 standards, and in correlation with manufacturer’s specifications.

We submit that AIMDs which are equivalent from the MR safety point of view with an existing predicate already determined to be ‘MR safe’ should not require direct clinical evidence if their MR safety status can be confirmed by using simulation and modelling testing. The rationale for this position is further elaborated in the MTAA Joint Industry Working Group (JWG) Position Paper *Evidence Requirements for Magnetic Resonance Imaging (MRI) Labelling of Active Implantable Medical Devices (AIMDs)*.
In section **Demonstrating the safety of IMDs in the MR environment**, under the heading **Instructions For Use** (page 104, 6th bullet point), the draft guidance states:

“Lack of quality imaging (image artefact) information (based on ASTM F2119). Suggested wording: […] This information may not be required if there are scan exclusion zoned defined.”

Image artefacts are routinely encountered during MRI scans and they do not pose a direct hazard to patients. The ASTM F2503-13 standard for marking (labelling) medical devices for safety in an MR environment states that “MR image artifacts are not considered to be a performance issue and so are not addressed in this international standard practice.” The ASTM F2119 standard, which is quoted in the draft guidance requirement, defines test methods for evaluation of MR image artefacts from passive implants; it is not a standard defining labelling requirements relevant to the MR environment. Therefore the MTAA recommends that the 6th bullet point on page 104 of the draft guidance be replaced with a requirement to include a general cautionary statement in the IFU to indicate that image artefact and distortion can result for the device and that these factors should be considered when interpreting the MRI images.”

In section **Demonstrating the safety of IMDs in the MR environment**, under the heading **Patient card** (page 105), the draft guidance states: “The manufacturer should provide a patient card to all patients with such implants [Implantable Medical Devices (IMDs)]”. The MTAA does not support the requirement for patient cards. Manufacturers of IMDs should be able to decide whether to supply a patient card or use other means for providing essential product information, including MRI safety status. The chosen medium should be appropriate for the type of implant in accordance with the relevant Essential Principles.

Furthermore, changes to the regulatory approval for MR conditional labelling based on retrospective validation may occur after the initial implantation of a device and that could make the initial product information provided on a patient card obsolete - e.g., MRI status may be upgraded from ‘MR unsafe’ to MR conditional’. In such situations, only the product information maintained in manufacturers’ own systems reflects the true status of the product, and it should be available online for easy reference by treating clinicians and radiologists should and MRI scan be required.

The MTAA is committed to work together with the TGA towards finalising the clinical evidence guidelines for medical devices to ensure patient safety. We welcome the opportunity to further discuss any outstanding issues with representatives of TGA’s Medical Devices and Product Quality Division.