AI/ML in Medical Devices Premarket Requirements - TGA Perspective

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Acknowledgement of Country

I would like to acknowledge the Traditional Owners and Custodians of the lands on which we meet today and pay my respects to Elders past and present.

I would like to extend that acknowledgement and respect to any Aboriginal and Torres Strait Islander peoples here today.

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- Is AI regulated?
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- Labelling
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TGA's regulatory framework

Best practice principles

- Risk-based approach to regulation

- Continual improvement by ongoing review of regulatory structures and processes
  - Recent consultations:
    - Clinical decision support system (CDSS) regulation
    - Electronic Instructions for Use (eIFU)
    - Companion diagnostics

- Align with national and international regulatory principles and best practices.
  - Reduce regulatory burden on industry.
  - Fit-for-purpose regulatory system responsive to latest regulatory science.

International Medical Device Regulators Forum (IMDRF)

- Alignment of guiding principles

- Continued participation in Artificial Intelligence / Machine Learning Working Group and Software as a Medical Device Working Group
- IMDRF published
  - (Draft) “Medical Device Software: Considerations for Device and Risk Characterization” (consultation closed 2 May 2024)
  - “Principles and Practices for Software Bill of Materials for Medical Device Cybersecurity” in April 2023
  - “Principles and Practices for the Cybersecurity of Legacy Medical Devices” in April 2023
  - “Machine Learning-enabled Medical Devices: Key Terms and Definitions” in May 2022

Specialities leading the charge on AI

Image processing

- Radiology
- Dermatology

…have been early leaders in developing products

Specialty colleges have published best practices on AI in medical devices

- RANZCR Ethical Principles for AI in Medicine
- RANZCR Position Paper on the Regulation of Artificial Intelligence in Medicine
- ACD Position Statement – Use of AI in Dermatology in Australia
- ACD Consensus Statement – Minimum Labelling Requirements for Dermatology AI-based Software as Medical Device

International standards

Best practices

- Use of international medical device standards (e.g. ISO 13485 for QMS and IEC 62304 for Software Life Cycle Processes) to align requirements across jurisdictions.
- If applicable, software validation should include testing against basic safety and essential performance in product (vertical) standard.
- Horizontal industry-agnostic standards such as ISO/IEC 42001 (AI management systems) and ISO/IEC TR 24027 (Bias in AI systems) can inform best practices on technology requirements, design, verification and validation, and risk and change management.

Artificial intelligence – some general observations

- Many new products – lots of diversity in how AI is used.
- AI is often supplied as part of an “ecosystem” – sometimes components are from different suppliers.
- AI is not always immediately visible in the design - requires extensive engagement with the supplier to elicit details of all architectural components.
- Many developers who include AI in their device are new to regulation – often validation artefacts are lacking or not provided at all.
- Data for training/testing of the AI is often not related to use case population or too small to be valid.
- The scope of this talk includes AI used in both standalone software (SaMD – informational output) and medical device software more broadly (including software driving hardware medical devices)

Is AI regulated?

How the medical device framework applies to AI

AI is a medical device when it is used for :

diagnosis, prevention, monitoring, treatment, alleviation of disease, injury or disability

See legislative definition of medical device in section 41BD of Therapeutic Goods Act 1989.

Which digital / software products are regulated as medical devices ?

Software is a medical device when the manufacturer intends for its product to be used for **diagnosis, prevention, monitoring, treatment, alleviation of disease, injury or disability**

It's a rather wide definition – includes **mobile apps, cloud, AI and through to software that runs dedicated medical devices**

Depending on the **intended purpose,** a particular product could be

- **Software as a medical device** (SaMD) – regulated by the TGA, OR
- SaMD **carved out from TGA regulation,** OR
- **Consumer health software** – not regulated formally

When is software regulated as a medical device?

This means:

- digital - software on **any computing platforms** (computers, tablets, smartphones, browsers);
- software that is **part of a medical device** - is regulated as part of that device;
- apps that **control a medical device** - are regulated as an accessory or a device;
- apps that **rely on medical device hardware** in addition to a general computing platform
(e.g. sensors) - are part of a medical device.

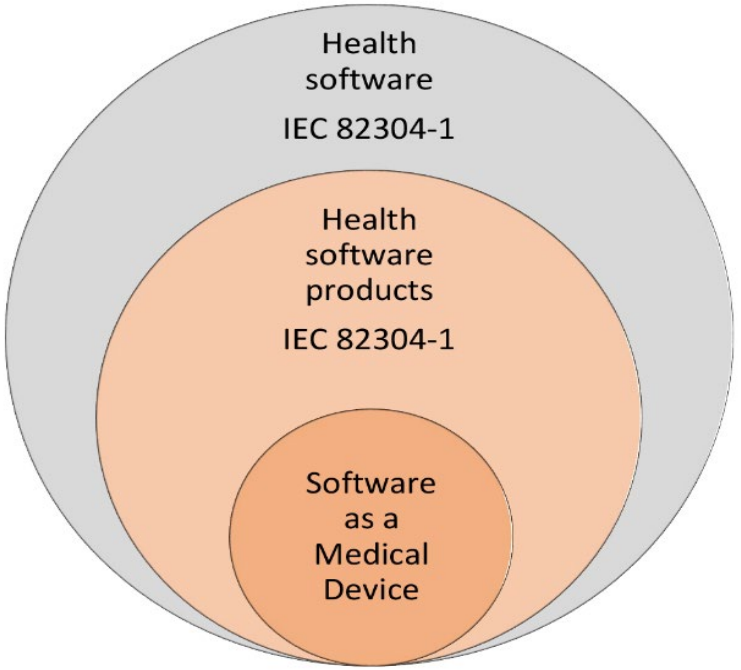
TGA carves out particular software from regulation as a device

- If the device presents a **low risk to safety**

OR

- If **alternative oversight schemes** are in place

- The scope of ‘health software’ is broader than ‘medical device software’
- **Most health software is not a medical device and is not regulated by TGA**



Examples of software “carved-out”

- **Consumer** health products - health preventative and management devices that **do not provide specific treatment suggestions**
  - e.g. consumer products for monitoring heart rate or rhythm solely for general wellness or fitness purposes
- **Enabling** technology - for telehealth, remote diagnosis, healthcare or dispensing
- **Digitisation** - simple dose calculators and Electronic Patient Records
- **Analytics** - population based
- **Laboratory Information Management Systems**
- **Some aspects of Clinical Decision Support Software –** e.g. if they are not intended to replace health professional judgement in making a diagnosis or treatment decision

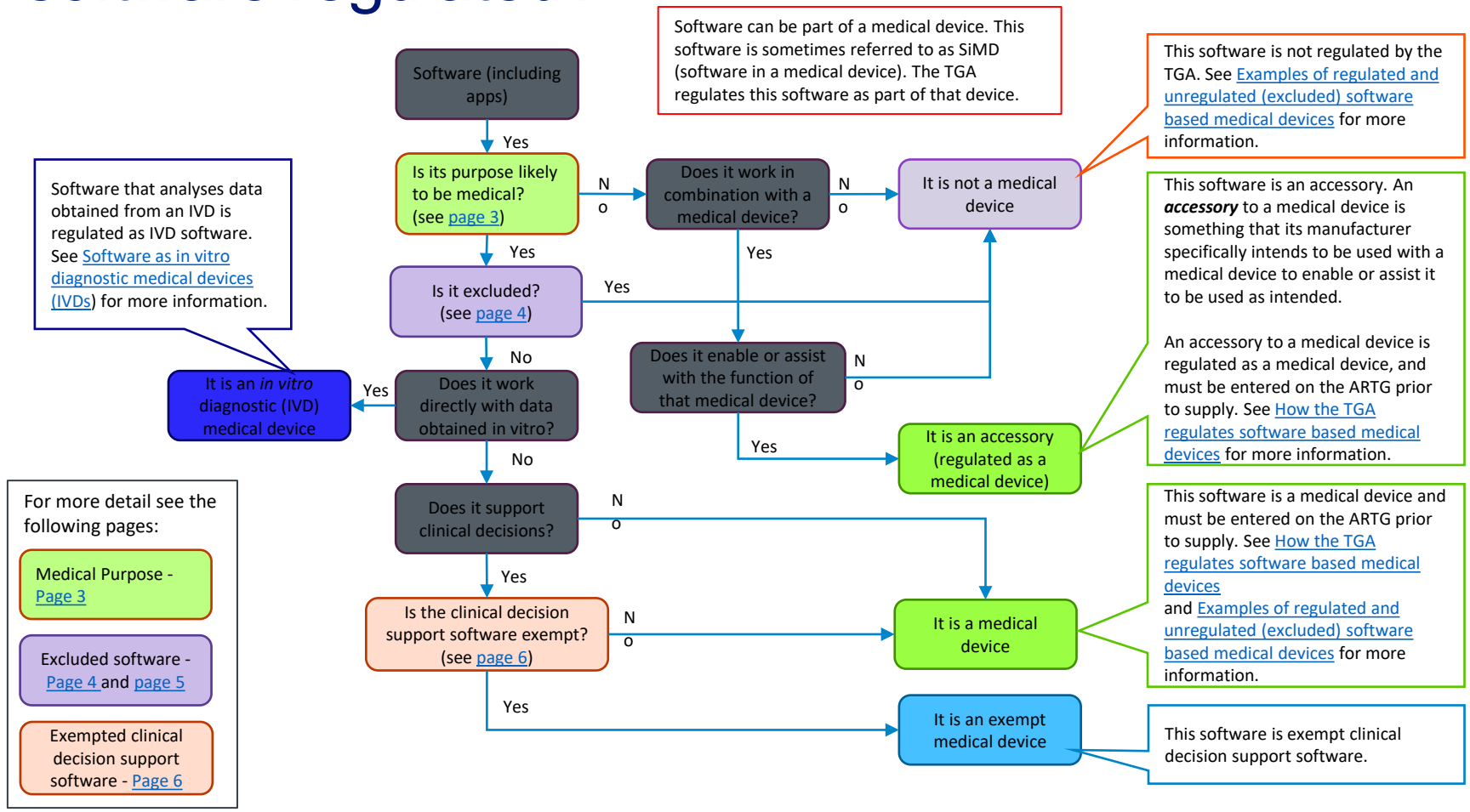
Is it a medical device?

Exclusion and exemption

- Beware of feature creep turning excluded products into medical devices:
  - AI-based alarms or alerts in electronic health record
  - AI-based remote monitoring in communication software for telehealth
  - AI-based calculation of dosage, risk, predictive or prognostic score

- Beware of feature creep turning wellness products into medical devices:
  - Sensor-based measurements to aid diagnosis, monitoring, or track progress of treatment of a disease or condition.

Is my software regulated?



So if I am a developer, what do I do?

- Refer to guidance on whether your product is regulated by the TGA

Many health software products are **not medical devices**

- If it is an **in-house or bespoke software product and it is a medical device**:
  - Determine the risk **classification**
  - Hold **evidence of compliance** with the **essential principles** for safety, quality, and performance
  - Obtain **TGA or comparable overseas regulator (e.g. MDSAP)** for assessment of technical files, inspection of QMS, manufacturing site
  - Apply to the TGA for regulatory approval
  - Follow post-market requirements

AI/ML in medical devices

Considerations

- Data driven nature of device mechanism

- Data management
  - Training data – related to Design & Development
    - Can be labelled with ground truth or not
    - Supervised learning vs unsupervised learning
    - Synthetic data
  - Testing data – related to Verification & Validation
    - Should be rigorously labelled with ground truth by competent expert
    - Should be independent to training data – prevents spurious finding – increases generalisability

AI/ML in medical devices

Considerations

- Software regulation plus:
  - Good Machine Learning Practice for Medical Device Development: Guiding Principles (FDA, MHRA, Health Canada)
  - Current work item in IMDRF AI/ML WG – Consultation draft June 2024
  - Guiding principles vs best practices (standards)

- Rapidly evolving field – e.g. generative AI

- Potential to drive novel device types e.g. brain-computer interface

AI/ML in medical devices

Main risks

- Accuracy and reliability including human factors consideration and human interpretability of the model outputs
- Generalisability of performance across the intended patient population
- Control of data management practices for model training and testing
- Management of bias and performance degradation across lifecycle

Device characterisation

Intended use and device description

Intended use should include:

- Medical purposes
- Intended conditions or diseases
- Intended patient populations
- Intended users
- Intended use environment
- (Contraindications)
- How inputs and outputs align to clinical workflow

Device description should include:

- Further info on medical problem or objective
- Further info on context of use
- Function or use in clinical workflow (e.g. aid in diagnosis, image segmentation, triage), level of autonomy
- Change management (e.g. installation platforms and update functionality)

Risk classification

(and pitfalls)

- Classification of software-based medical devices is based on:
  - Medical purpose (e.g. diagnosing, monitoring, recommending treatment, providing therapy)
  - Risk of condition or intervention (e.g. death, severe deterioration, serious condition)
  - Autonomous or adjunctive use (i.e. HCP making decision)

- Also pay attention to Reg 3.3(5):

  If a medical device is driven, or influenced, by an item of software, the software has the same classification as the medical device.

See TGA guidance: Classification of active medical devices (including software-based medical devices)

Classification of medical devices – risk of harm

Classification	Class I	Class Im	Class IIa	Class IIb	Class III
Risk	Low risk	Low-Medium risk		Medium-High risk	High risk
Software Example	Hearing loss diagnosis	Goniometer	ECG app	ICU breathing monitoring	Melanoma diagnosis to consumer

SaMD Validation (IMDRF N41 2017)

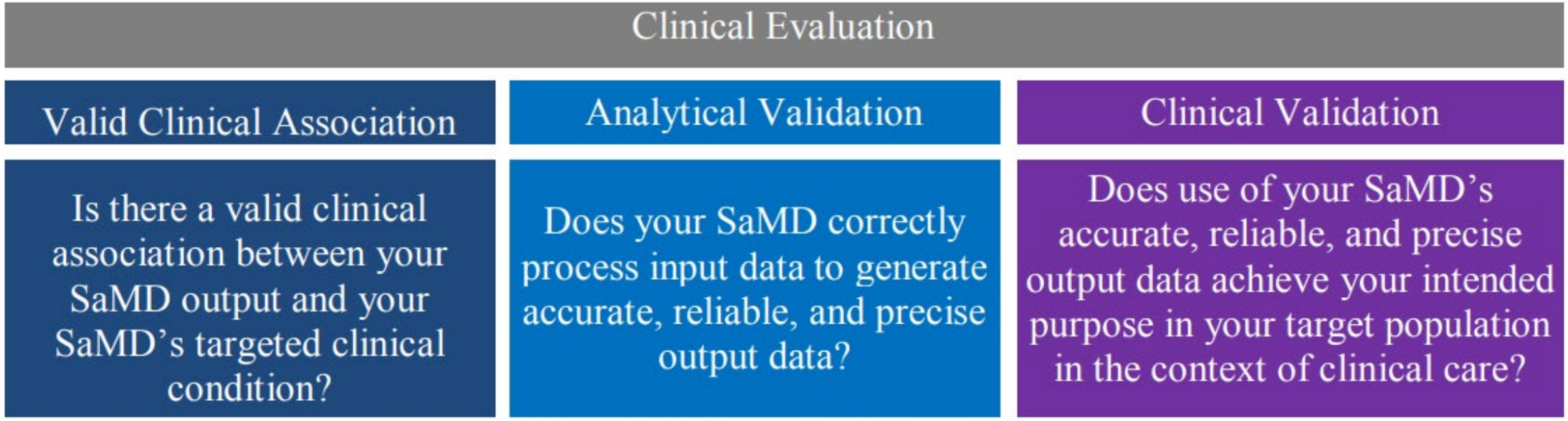


Figure 1 - Clinical Evaluation Process

Analytical validation – analogous to bench and animal testing – worst case testing (spans entire spectrum of intended use)

Clinical validation – analogous to clinical trials – intended use in clinical environment – representative but not worst case

Bias – Clinical Study vs Machine Learning contexts

Considerations common to both clinical studies and machine learning:

- Bias related to generalisability of results to entire spectrum of intended patient population, i.e. external validity
  - Prevalence aspect – rare disease or subgroups will be represented proportionately less in datasets

Considerations with greater impact on machine learning than clinical studies:

- Bias related to post-hoc or exploratory analysis of datasets yielding chance or spurious findings – similar to “alpha” error in clinical studies i.e. concluding there is a difference between groups when there is none
- Bias related to unsupervised learning (e.g. generative AI) – learning from “real world” data which may fall short of standard of care e.g. electronic health record data – thus amplifying health inequities

Bias

Mitigation by transparency

- Also risk of overfitting – model output could be based on spurious learned relationships – mitigated by training datasets being independent of test sets +/- external validation.

- Ensuring transparency of these potential biases:
  - Labelling requirements are being recommended in position statements from specialty colleges e.g. RANZCR, ACD (dermatology) – include characteristics of training and test data sets, algorithm design, clinical validation study design and results
  - Basis for model output to the extent possible, either in labelling or during software use

Clinical evaluation

Clinical validation +/- Clinical utility studies

- Accuracy of software output may not be adequate:
  - Consider reader study if adjunctive use
- Level of external validation should be proportionate to risk and classification
- Novel use in clinical workflow or use of novel biomarkers may require clinical utility studies showing benefit in patient outcomes beyond accuracy
- Generalisability to Australian population needs to be justified.

Labelling

AI/ML aspects

- Clear documentation of AI/ML algorithms:
  - Training and testing data
  - Clinical validation study design and results
  - Intended use

- Labelling requirements from specialty colleges:
  - RANZCR Position Paper on the Regulation of Artificial Intelligence in Medicine
  - ACD Consensus Statement – Minimum Labelling Requirements for Dermatology AI-based Software as Medical Device

Quality management system

AI/ML aspects

- Product realisation
  - Planning includes consideration of risks of bias and performance degradation across product lifecycle.
  - Design & Development (D&D) planning includes competent experts for labelling datasets
  - D&D and Verification & Validation (V&V) include accuracy and reliability; useability; test dataset independent of training dataset; performance generalisable across intended patient population
- QMS
  - Records include procedure for correct labelling of training and test datasets in case of supervised learning, and version control of all datasets
- Measurement, analysis and improvement include product monitoring

Quality management system

Clinical considerations of AI/ML aspects

- Management responsibility - QMS planning - risk management process includes clinical safety and performance considerations
- Resources management - Human resources - includes clinical expertise e.g. proper triaging of clinical related complaints
- Product realisation - Planning of product realisation - risk management coverage of clinical risks
- Product realisation - D&D planning - includes clinical expertise e.g. clinical labelling of training and testing datasets for ML based devices, clinical utility and useability considerations
- Product realisation - D&D validation - clinical validation
- Measurement, analysis and improvement - Feedback, complaint handling, monitoring and measurement of product - includes active and passive post-market monitoring appropriate for the intended use, proper triaging of clinical related complaints

Pre-determined change control plan – work underway

Guiding principles from FDA/MHRA/HC

- Focused and Bounded
- Risk-based
- Evidence-based
- Transparent
- Total Product Lifecycle (TPLC) perspective

The TGA is looking at this with a view to international alignment.

Contact us

- TGA partnership with ANDHealth (especially for new developers): https://www.andhealth.com.au/partners/tga
  - Digital health webinars
  - Office hour sessions

- Digital devices team: digital.devices@tga.gov.au

- General medical device enquiries: devices@tga.gov.au

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Exhibition booth **No.1**

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