Post Activation of Human Biomedical Research Act: Compliance & Risks

Yeo Jing Ping / SingHealth

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CRCS Forum

Human Biomedical Research Act: What it means for you

Agenda

- Introduction
- Importance of compliance and compliance challenges
- Risk of non-compliance vs harm minimization
  - Informed consent
  - De-identification
  - Safety reporting
  - Management of incidental findings
- Conclusion

Key Challenges in Research Process

1

Informed consent

- *Understanding of information*
- *Communication of risk*
- *Decisional authority for consent to research*

2

Responsible conduct of research

- *Collaborative Science*
- *Conflicts of Interest and Commitments*
- *Data Acquisition, Management, Sharing and Ownership*
- *Human Research Protection*
- *Lab Animal Welfare*
- *Mentoring*
- *Peer Review*
- *Publications Practice and Responsible Authorship*
- Research Misconduct

3

Proper conduct of research

- *Conducting study according to protocol approved by IRB?*
- *Any deviation from protocol?*
- *Are the deviation documented?*
- *Personally conduct or supervise the described investigation?*
- *Informing any potential participants that the test article(s) (i.e., drugs or devices) are being used for investigational purposes?*

Compliance and Quality of Clinical Research

HUMAN SUBJECT PROTECTION

DATA INTEGRITY

Achieved by being compliance with applicable laws and regulations of clinical research

Human Biomedical Regulatory Framework

1 Nov 2017 in force

HBRA

Human biomedical Research Framework

- Regulates the conduct of Biomedical Research
- Covers 2 areas:
  - Human subject research that have certain intended purposes and involve certain methodologies
  - Restricted and prohibited research

Human Tissue Framework

- Regulates dealings in human tissue
- Prohibits commercial trading in human tissue

Exclude :

- Service evaluation
- Clinical audit
- Surveillance
- Outbreak investigation
- Psychological responses +behaviors
- Measure human intelligence
- Public health research on infectious disease (Infectious Diseases Act)

Exclude :

- National registry of diseases of health information (National Registry of Disease Act)
- Collection of health info for stats purpose (Statistics Act)
- Clinical trials of Health products (Health Products Act)
- Clinical trials of medicinal products (Medicines Act)

HBRA Implementation Plan

Human Biomedical Research Act (HBRA)

- **Passed by Parliament in August 2015**
  …being brought into operation gradually in phases
- **Implementation Plan & Schedule**

➢ **<u>Phase 1</u>: Administrative provisions** – ***Activated on 1 Jul 2016***
➢ **<u>Phase 2</u>: Prohibition against commercial tissue trading** – ***Activated on 1 Jan 2017***

➢ **<u>Phase 3</u>: Regulation of Human Biomedical Research** – ***Activated on 1 Nov 2017*** → ***(Savings and transitional provisions ended <u>1 Nov 2018</u>) Exemption regulation ending 31 Oct 2019***

HBR Framework

- ✓ Functions and Duties of RI
- ✓ Functions and Duties of IRB
- ✓ Approval and Conduct of Restricted Research
- ✓ Amendment to Third, Fourth and Fifth Schedules of the HBRA → In response to stakeholder concern and feedback on consent requirements & rHBR scope

➢ **<u>Phase 4</u>: Regulation of Research Tissue Banking** – ***Target Q1 2019***
➢ Duties of Tissue Bank (S34-36) and other controls to be prescribed

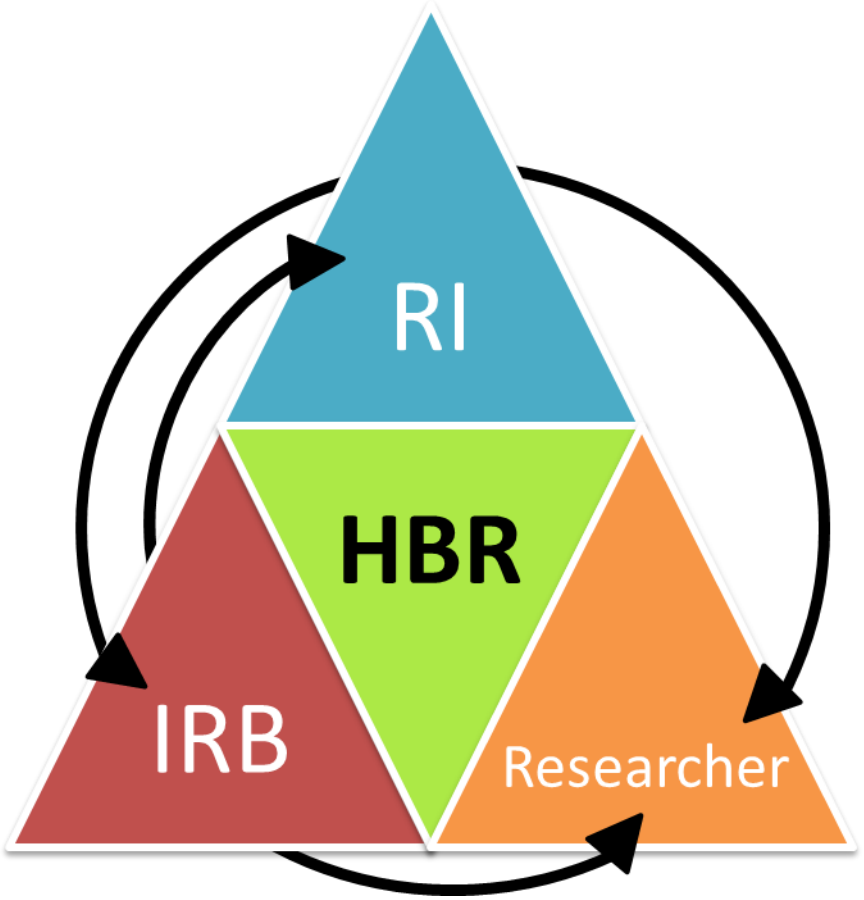
HTR Framework

- ✓ Restrictions on activities relating to human tissue (S37)
- ✓ Compelling person to donate tissue (S38)
- ✓ Restriction on disclosure of information on tissue donor (S39)
- ✓ Savings & transitional provisions for legacy human biological material (S64)

Reference: Stakeholder consultation on Draft Human Tissue Framework (2 March 2018)

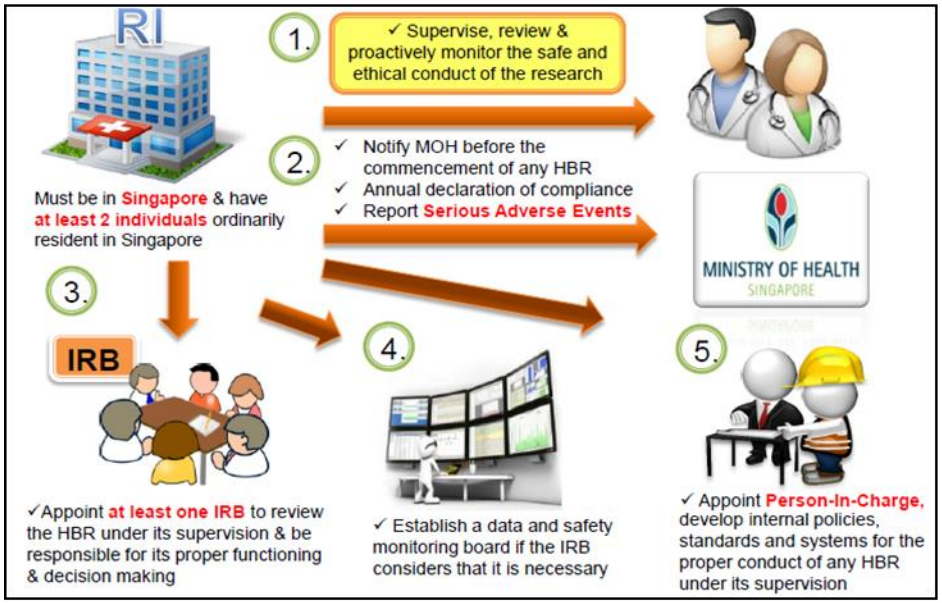
Achieving Compliance to HBRA

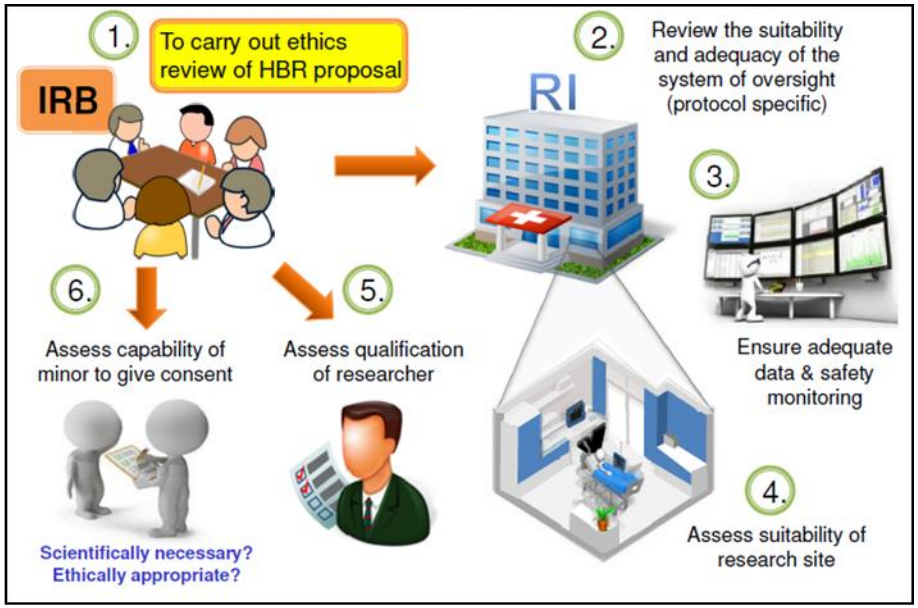
- Interlocking system of self-accountability
  - *Between RI, IRB and researchers*
- Ensure understanding of regulations and roles and responsibilities
- Ensure researchers have access to publically available materials about HBRA

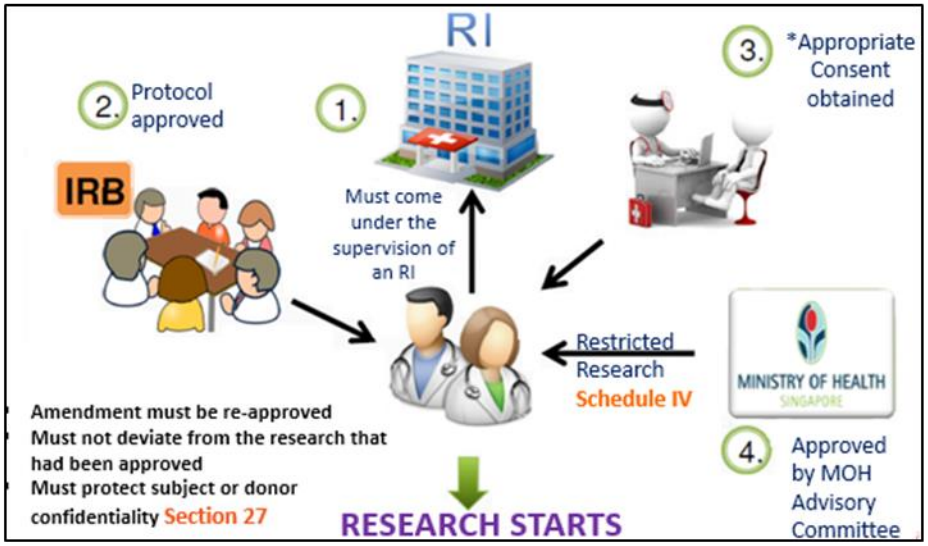


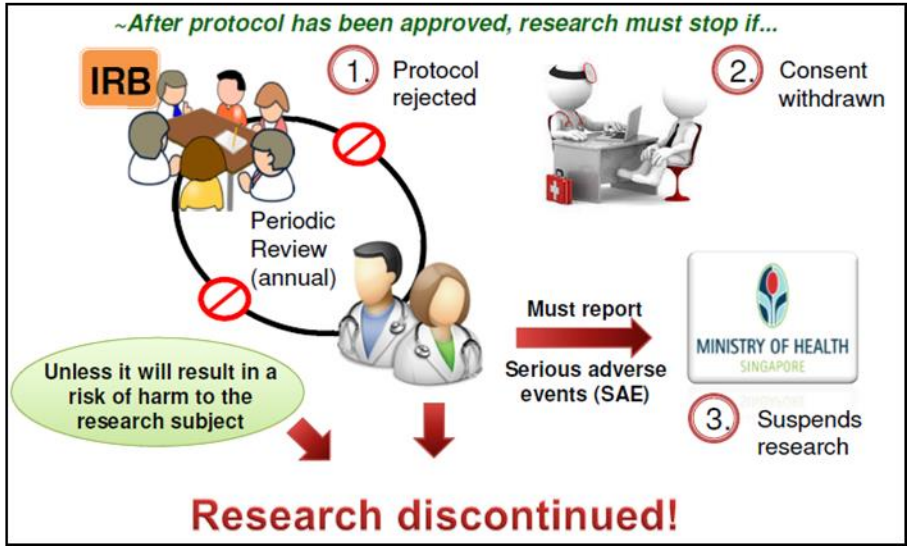
Functions and duties

sections 23, 24 HBRA







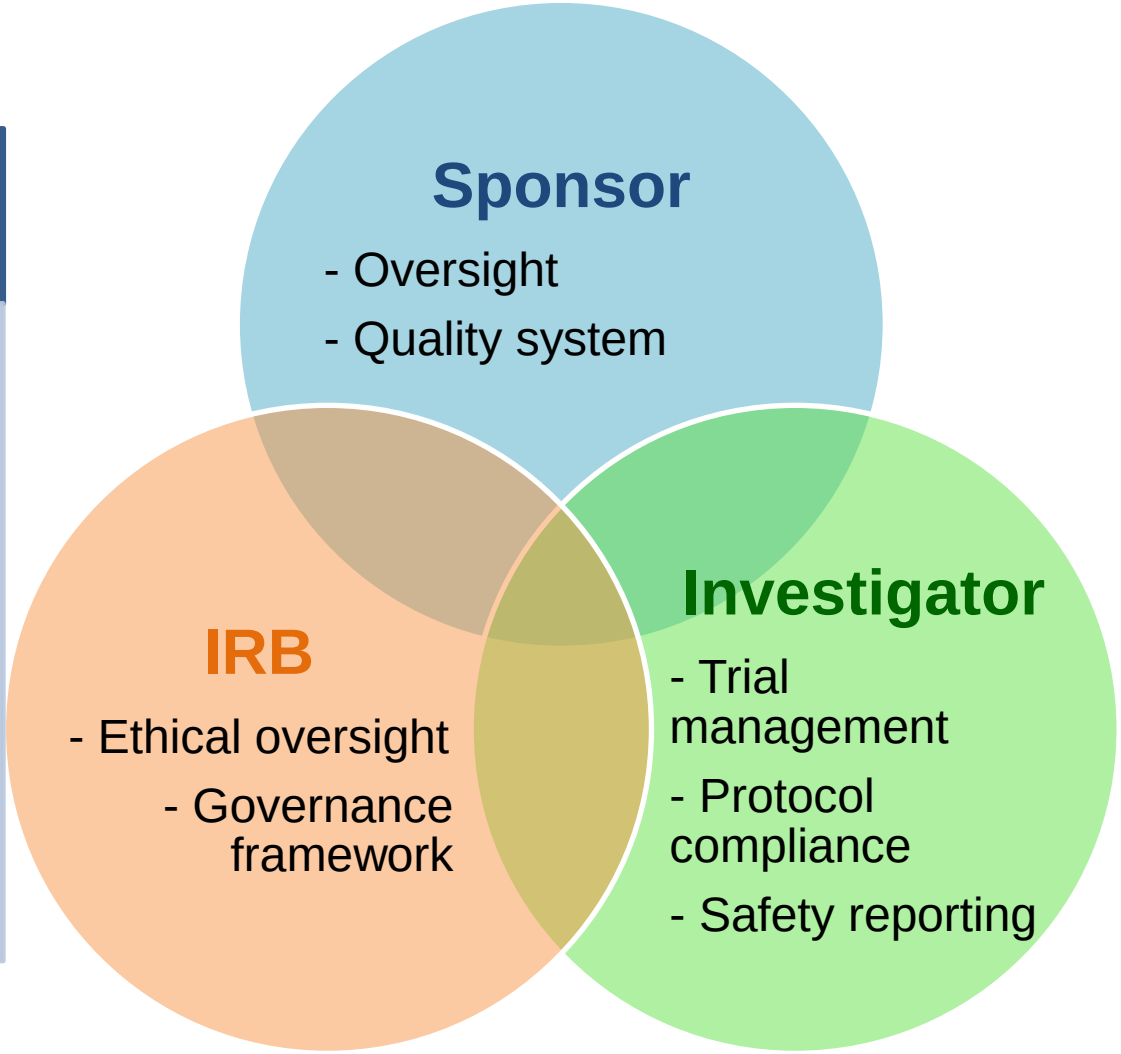


Compliance Challenges

Commons Inspection Findings

- Non compliance with protocol
- ISF not maintained
- Lacking PI oversight
- Missing source documentation
- Informed consent not taken
- Failure to report safety events

FDA and EMA findings



Why is there risk of non-compliance?

- Research and HBRA are complex
- Clinician – investigators are busy
- Administrative support is sometimes lacking
- Education is non-mandatory

Risk factors for noncompliance

- Inappropriate study conduct –especially with sensitive research
- Insufficient involvement of investigators in study conduct
- **Inappropriate handling of informed consent**
- Missing IRB approval
- **Inappropriate handling of SAE, noncompliance reporting**
- Inadequate maintenance of accurate records
- **Mishandling of identifiers**
- **Inadequate handling of incidental findings**

Risk Management Considerations

- Ensuring regulatory compliance
  - Institutions policies and procedures
- Monitoring
  - Compliance of researchers during conduct
  - HBRA
  - IRB continuing review
- Training/Education
  - IRB
  - Investigators, study coordinators
- Safety reporting
  - Adverse events reporting
  - Trend analysis
- Adequate support
  - IRB workload
  - Proper culture for protection of human subjects
  - Resources
  - Information technology


INFORMED CONSENT

Appropriate Consent accordance to HBRA

section 6, 12 & 14

Human Biomedical Research

General rule-

"Appropriate consent" must be obtained:

1. In writing;
2. From the subject personally;
3. After subject is given full explanation on research & expected involvement
4. Prior to subject involvement (intervention OR use of ID material OR ID health info)

Withdrawal of consent:
Consent may be withdrawn at any time by the subject or his proxy

N.B. Withdrawal does not affect any research info or data obtained before the consent is withdrawn

Human Tissues

Withdrawal of consent:

Consent may be withdrawn at any time by the subject or his proxy if :

1. the tissue is individually-identifiable and has not been used for the research; or
2. the tissue is individually-identifiable and has been used for the research but it is practicable to discontinue further use of the tissue in research

N.B. Withdrawal does not affect any research info or data obtained before the consent is withdrawn

Adapted from MOH stakeholder consultation slides, CRP-CRCS 2016

Exemption from Appropriate Consent for use of Biological Material /Health Information collected before 1 Nov 2018

1

- ✓ Savings and transitional (S&T) period for HBR has ended on 31 Oct 2018. This means that moving forward, appropriate consent (in accordance to HBRA) must be obtained for the use of identifiable HBM/HI in HBR.
- ✓ On 31 Oct 2018, MOH issued an exemption to allow the use of identifiable HBM/HI without appropriate consent until 31 Oct 2019 if:
  - ❖ the individually-identifiable HBM/HI was obtained before the end of S&T (i.e. before 1 Nov 2018);
  - ❖ there is documentary evidence that the research subject had given relevant consent before end S&T for the use of individually-identifiable HMB/HI in research; and
  - ❖ the relevant consent was not withdrawn at any time before the end of S&T.

To note that Exemption will expire at end 31 Oct 2019

Adapted from MOH POC 15 Nov 2018

Exemption from Appropriate Consent for use of HBM/HI collected before 1 Nov 2017

2

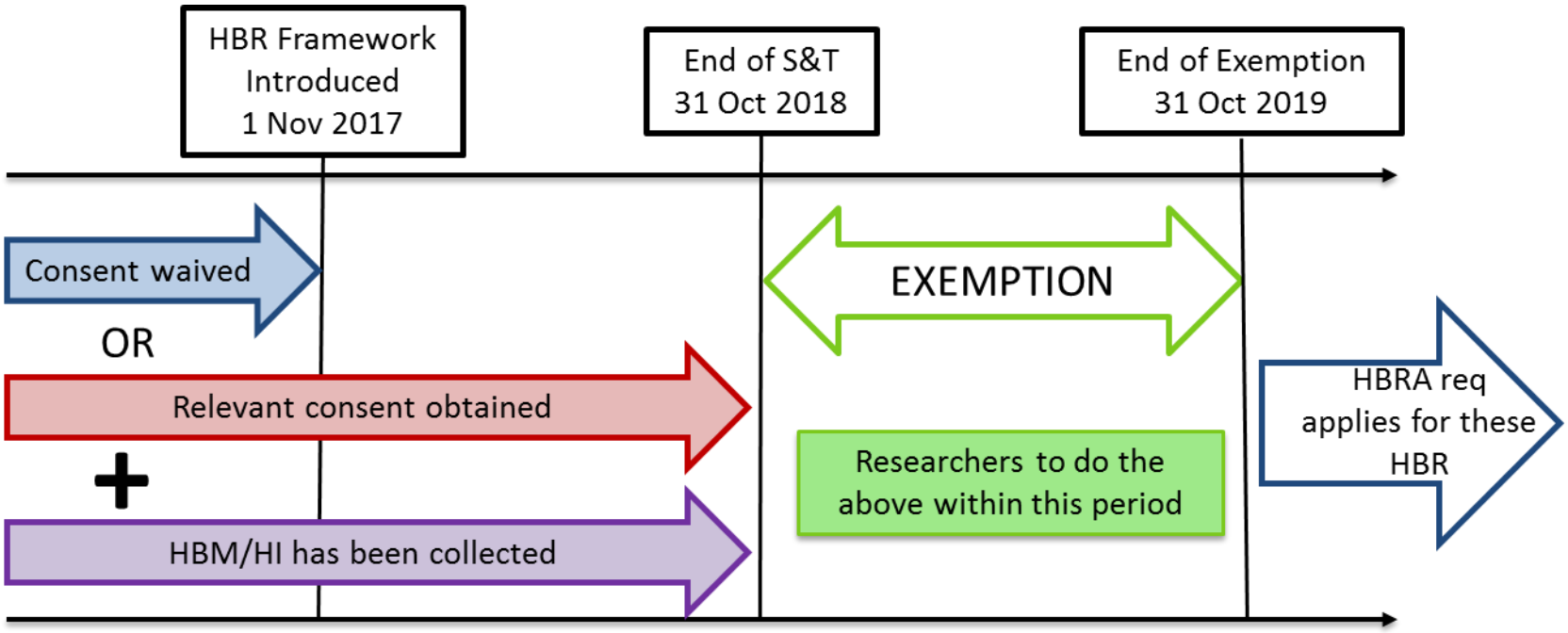
- ✓ The exemption on appropriate consent for use of identifiable HBM/HI obtained before the end of S&T also applies to HBR where the ethics committee has waived the requirement for consent before 1 Nov 2017 on the following grounds:
  - ❖ the research cannot reasonably be carried out without the use of the HBM/HI in an individually-identifiable form;
  - ❖ the use of the individually-identifiable HBM/HI (as the case may be) involves no more than minimal risk to the research subject; and
  - ❖ the waiver concerned will not otherwise adversely affect the rights and welfare of the research subject.

To note that Exemption will expire at the end of 31 Oct 2019

Adapted from MOH POC 15 Nov 2018

MOH : Extension of Grace Period for 1 year

- The exemption will give researchers more time to do the following:
  - ❖ Seek appropriate consent (in the presence of a witness) from the subjects or seek new waiver of consent from IRB in accordance with HBRA requirements if the study involves use of identifiable HBM and HI beyond 31 Oct 2019;
  - ❖ De-identify HBM or HI by 31 Oct 2019 for the use beyond 31 Oct 2019; or
  - ❖ Complete study by 31 Oct 2019



Reality Check: Informed Consent Issue

Unsure whether the study ICF meets HBRA requirements

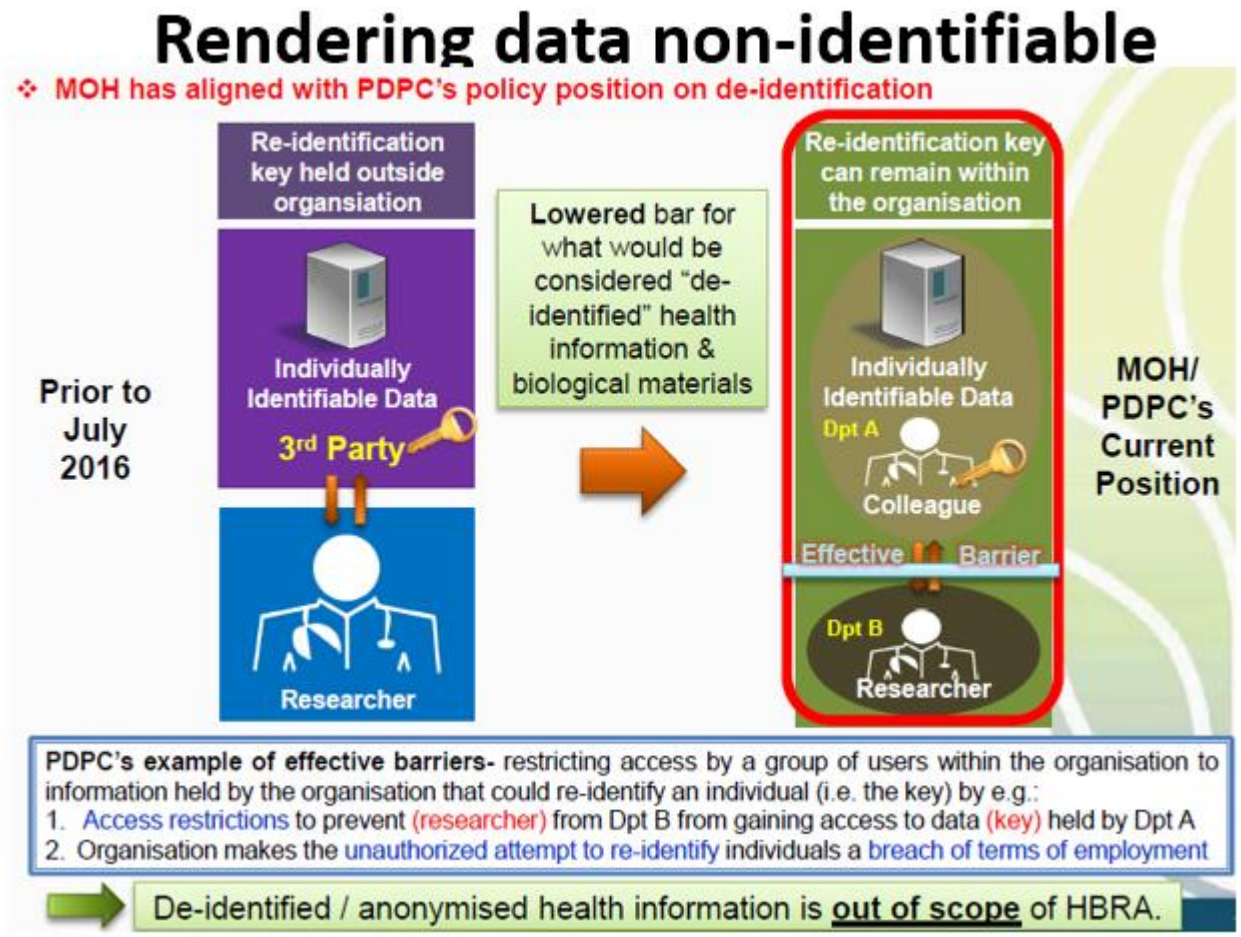
Is the maid allowed to sign on behalf of the legal guardian after a written confirmation in the form of a letter from the legal guardian

I am uncertain whether the present study falls under the scope of HBR even after referring to the HBR checklist.
The study seems to meet 1,2, 3 but not a, b, c

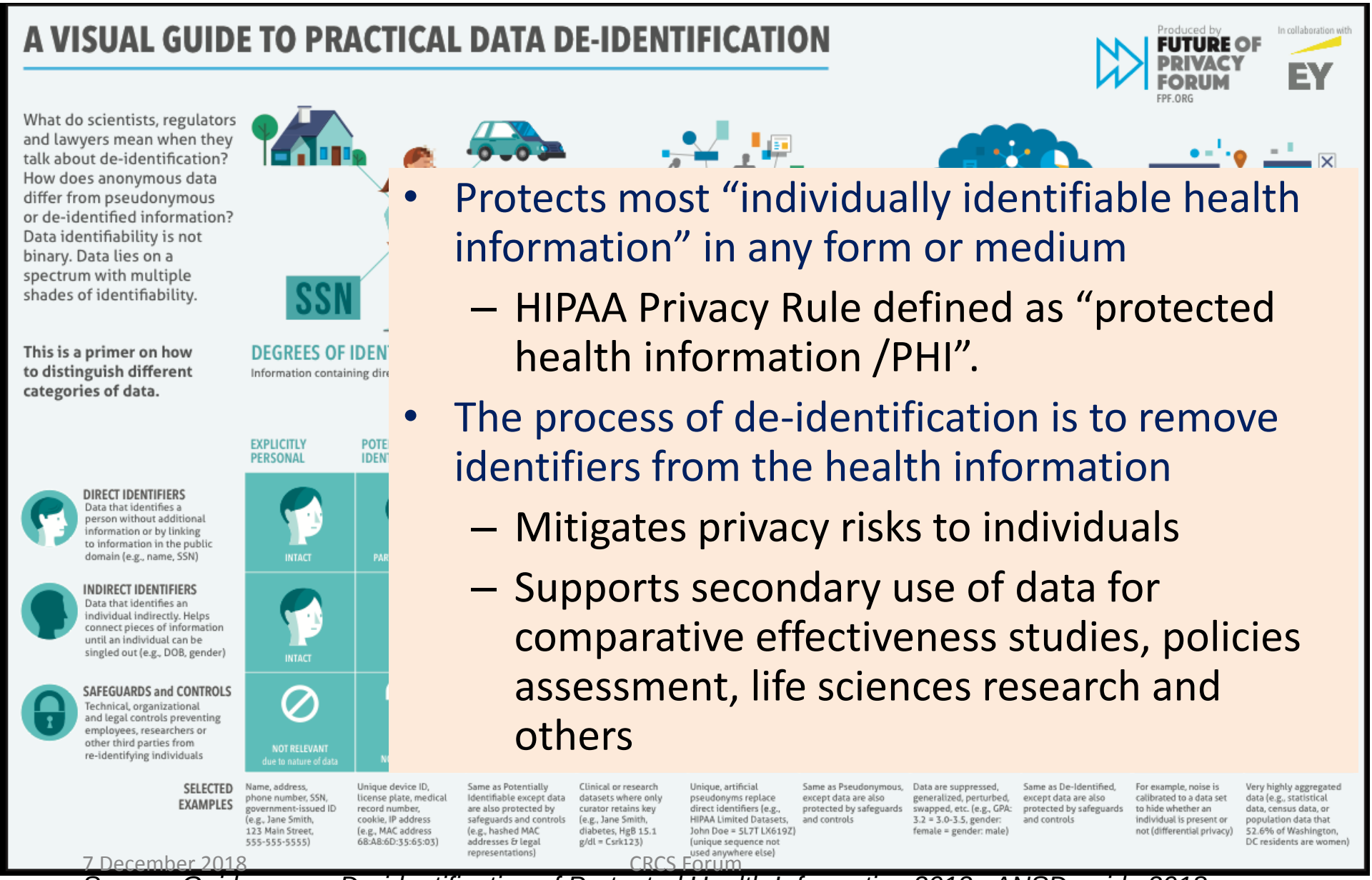
I am not able to re-consent the patient as there is no follow up. I cannot de-identify the data as I need to know the patients in case of safety issue

De-identification

- MOH refers to “individually identifiable” and “non-identifiable” in definition of research, section 27, 28, 29



Understanding of De-identification



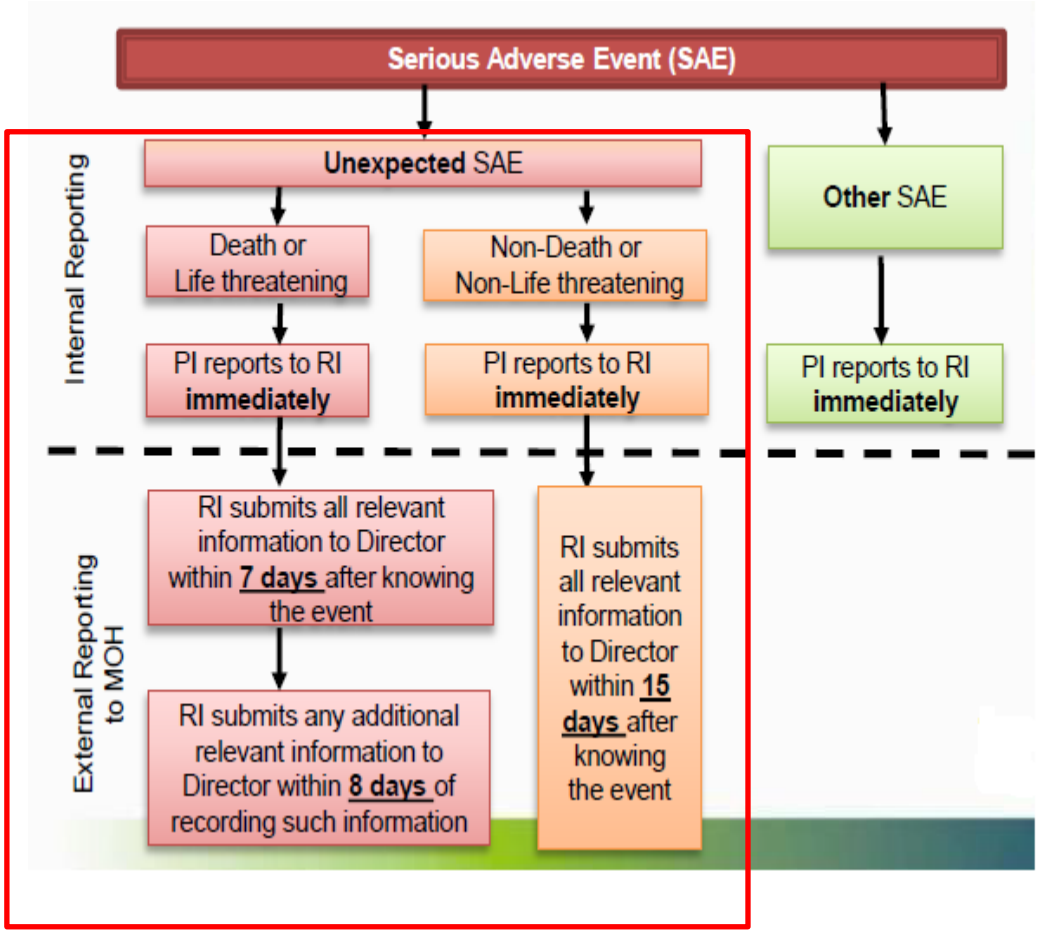
- Protects most "individually identifiable health information" in any form or medium
  - HIPAA Privacy Rule defined as "protected health information /PHI".
- The process of de-identification is to remove identifiers from the health information
  - Mitigates privacy risks to individuals
  - Supports secondary use of data for comparative effectiveness studies, policies assessment, life sciences research and others

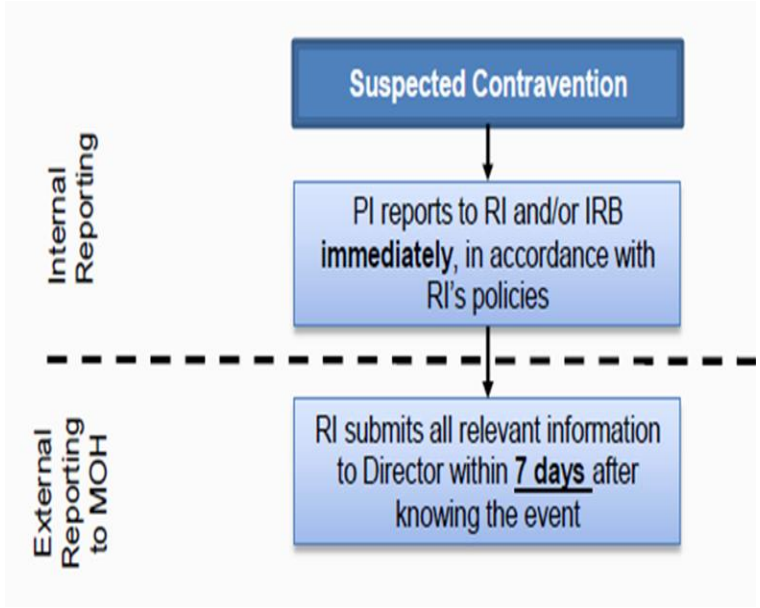
Source: Guidance on De-identification of Protected Health Information 2012 ; ANSD guide 2018

Reality Check: what is de-identification?

- **For existing study whereby all the identifiable data and specimens are collected**
  - ✓ What is de-identification through a trusted third party?
  - ✓ Who will be the de-identification agent and data custodian?
- **What is de-identified patient information**
  - ✓ Removal of all patient ID from the investigation file?
  - ✓ What about the consent form containing patient detail?

SAE Reporting and Suspected Contravention Reporting





- Currently not aligned with that for HSA regulated studies
- *MOH has indicated plan for alignment*

Reality Check: Handling of reportable events

- Investigator are responsible for identifying and reporting non-compliance events.
  - If it meets criteria of reporting, this will be reported to IRB
  - Investigator may also ensure reporting to a monitoring entity (such as sponsor, or DSMB) as described in protocol
- Understanding of reportable SAE event:
  - "unexpected" when vast majority of SAEs occurring in the context of research are "expected".
  - "related" or "possibly related" SAEs, where again, majorities will indicated as "unrelated".

Investigator's evaluation of event is critical.
Balance and checks should be in place over time.

Handling of Incidental Findings

- HBRA requires research team to have a clear informed consent material that convey the plan for incidental findings management

HBRA section 12 (1)

(*m*) *whether the research subject would wish to be re-identified in the case of an incidental finding if the proposed biomedical research expressly provides for such re-identification;*

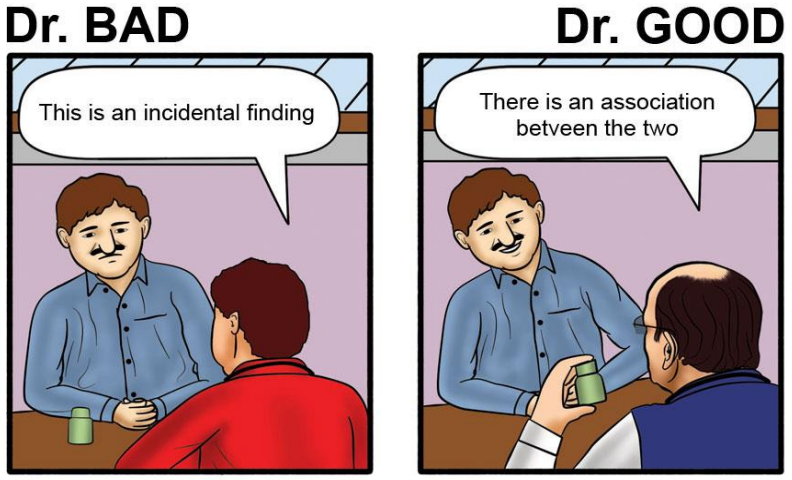
HBRA section 12 (2)

(*o*) *whether the donor or the person authorised to give consent under this Part, as the case may be, would wish to be re-identified in the case of an incidental finding if the future research expressly provides for such re-identification;*

Reality Check: Incidental Findings

- What is the procedures and resources required to handle incidental findings
  - An appropriate plan to evaluate or return IFs
  - A thoughtful consideration of whether, when, and how to incorporate participant preferences, and if researchers intend to return certain incidental findings
  - A clear policy outlining the follow-up assistance

Situation: An asymptomatic patient with early diabetes was found to have chronic blockages on 64 CT coronary scan



Lesson: In a study of Chinese adults with different glycemic status, using a noninvasive CAD diagnostic modality such as dual-source computed tomography coronary angiography, detected a markedly elevated risk of significant coronary stenosis with early diabetes in asymptomatic individuals. (Diabetes Care 2013 Mar 5. [Epub ahead of print])

Researchers – Minimise Risks and Protect Subjects Rights and Welfare

- Ensure research personnel are informed of their obligations
- Ensure protocols are compliance with ethical principles, regulatory requirements
- Perform procedures consistent with sound research design
- Protection of privacy and confidentiality
- Additional safeguards for vulnerable subjects
- Obtain appropriate informed consent (unless with waiver)

Reminder

- HBRA is important:
  - To protect the rights and welfare of subjects
  - To assure sound, reliable research
- The physicians, hospitals, IRB and AMCs are required to assure compliance . . .
  - when they fail, they face: fines, penalties
  - Cessation of all human research activities for researchers
  - Bad PR (and loss of future research volunteers)
- The Principal Investigator is:
  - Presumed to **know**, **understand**, and **comply** with all of the rules, regardless of available administrative support
    - Held ultimately accountable for everything he/she does and everything anyone else on the study team does

Conclusion

- **Safety and well** being of subjects always come first
- A **changing mindset** in the way research are conducted and managed will be vital - institution, researchers, IRB and rest of research community
- **Compliance** is part of ongoing process of continual quality improvement