Summary of updates to Proper Conduct of Research (PCR) SOPs
[Summary last updated: 11 November 2016]

In line with the Health Products Act (HPA) 2016, revised Medicines Act (MA) 2016 and the Human Biomedical Research Act (HBRA) 2015 gazetted, NHG Research Development Office (RDO) would like to inform about the following updates to the Proper Conduct of Research (PCR) SOPs.

Important Note:
(1) For Clinical Studies Regulated Under the Health Products Act and Medicines Act
\[\Rightarrow\] Revised regulatory requirements should be complied with from 1 Nov 2016.

(2) For Human Biomedical Research Regulated Under the Human Biomedical Research Act (HBRA)
\[\Rightarrow\] MOH has recently informed that the effective date of HBRA has shifted from Q1 to Q3 (July 2017) onwards. As such, while the policies have been updated to reflect the new requirements, a light touch approach will be taken on the implementation of these new requirements by researchers during this transition period.

\[\Rightarrow\] You may refer to our Qualite publication for a summary of the key differences between the pre-existing requirements and new HBRA requirements. Most changes pertain to informed consent practices in minors and cognitively impaired adults. The DSRB Informed Consent Form Template will be updated subsequently to include the additional elements stipulated in the HBRA.

1. 501-A02: Responsibilities of the Research Team

The definition of a qualified practitioner according to HPA and MA has been added (Item 2.g).

The key updates to PI’s responsibilities according to the revised regulations are:
   a) Assure that a qualified practitioner (PI or Co-investigator), who is registered with the appropriate professional board, is responsible for all research related medical decisions (Item 4.3)
   b) Ensure the appropriate type of approvals/ notifications/ acknowledgement have been obtained from DSRB and Health Sciences Authority (HSA) prior to study initiation (Item 4.4.a) and any trial suspension or termination is adhered to by all persons involved in the trial (Item 4.4.i)
   c) Assure that the individual obtaining consent is a qualified and trained personnel (Item 4.8.c)
   d) Ensure the further participation of the research subject or further use of the individually-identifiable biological material or health information of the research subject is immediately discontinued if the consent is withdrawn* by subject unless the immediate discontinuation will result in a risk of harm to the subject (Item 4.8.n)
   e) Provide an option to the subject for future recontact for specific reasons (e.g. future research participation, potential reconsent, further consent, incidental findings) (Item 4.8.n)

It is also the PI’s responsibility to ensure that translation of study documents is accurate and translation cert is maintained as appropriate according to DSRB policy.

Examples of study team members’ responsibilities have also been revised to be more concise for better understanding.

* The withdrawal of consent does not affect the research information obtained before the consent is withdrawn and such information may be retained and used for the research.
2. 501-A03: Training and Education

This SOP has been updated to clarify the term “Clinical Trial Certificate” that was used to describe studies regulated by HSA (Item 6.2). The minimum training requirements on Financial Conflict of Interests (Item 8.5) has also been specified in this SOP.

3. 501-B02: Pre-Study Activities

Information on the submission process for HSA regulated studies due to the revised regulations and the review of Clinical Trial Agreement has been updated on this SOP.

The definitions of Clinical Trial Certificate, Clinical Trial Authorization, Clinical Trial Notification, Clinical Research Material and Observational Trials according to the revised regulations are stated in this SOP (Item 3.b – 3.e, 3.j).

All clinical trials, excluding observational trials, involving a therapeutic/ medicinal product will require a Clinical Trial Approval (CTA), Clinical Trial Notification (CTN) or Clinical Trial Certificate (CTC) from HSA. A CTA/ CTC application may be submitted in parallel with DSRB application. A CTN application should only be submitted to HSA after written approval from DSRB has been obtained. A CRM notification is required if research materials/products (e.g. therapeutic products, medicinal products, medical devices, lab kits) are imported or locally manufactured (Item 7.1, 7.2 and 7.3).

Information pertaining to review of Clinical Trial Agreement and Budget has been removed as each Institution can determine their own review process.

4. 501-B03: Study Initiation

This SOP has been revised to clarify the requirement to obtain the appropriate approvals from HSA where required and elaborate on examples of tasks that can be listed on the delegation log.

For clinical trials regulated by HSA, the PI must ensure that a Clinical Trial Certificate (CTC) / Clinical Trial Authorization (CTA) / Clinical Trial Notification (CTN) / Clinical Research Materials (CRM) Notification (where applicable) must be obtained prior study initiation (Item 4.1).

The PI should delegate study-related tasks to qualified/ trained members of the research study team (Item 5.2). Examples of tasks that can be listed on the delegation log have also been amended for clarity (Item 5.3).

5. 501-B05: Documentation

This SOP has been updated with retention requirements for HSA-regulated studies (Item 4).

According to the new regulations, the essential documents should be retained until at least until the later or the latest, as the case may be, of the following:

a) the date where there is no more pending or contemplated application for registration under the Health Products Act of the therapeutic product(for a product licence for the medicinal product being tested in the clinical trial;

b) the expiry of 2 years after the last of such registrations is granted/after the last approval of such application for the medicinal product to be tested in Singapore;
c) where the clinical trial is terminated, the expiry of 2 years after HSA has been informed of the termination of the trial under regulation 12 of the Health Products or Medicines (Clinical Trials) Regulations 2016;
d) the expiry of 6 years after the conclusion of the clinical trial;
e) the expiry of such other period as HSA may direct in any particular case.

6. **501-B06 Investigational Product Accountability**

The definitions of Medicinal Product, Investigational Medicinal Product, Therapeutic Product, Investigational Therapeutic Product, Investigational Product, Investigational Device, Transitional Device, Investigational Product and Auxiliary Product have been defined in Item 2.a – 2.h of this SOP.

Record keeping requirement of Investigational Product (IP) and Auxiliary Product (AP) has been defined in Item 6 of this SOP.

IP/ AP should be labelled as per regulatory requirements. Any omission of any labelling elements should be submitted to HSA (Item 6.3.1). Additional requirements for labelling of medical devices are listed in Item 6.3.2 of the SOP.

Dispensing of IP/ AP has been revised to include the proprietary name or other description of the IP/AP dispensed and the Identification number (e.g. batch number, lot number) as required by the regulations (Item 8). The PI must ensure that only a study team member who is a qualified practitioner or a person who is assisting and acting under the instructions of, such individual, can administer the IP/AP (Item 8.2).

Documentation requirements of returns of IP/ AP have been defined in Item 10.1 of the SOP.

For Research Involving Controlled Drugs: If the IP/AP is a controlled drug, it is subject to the provisions specified in the Misuse of Drug Act. The PI and/or designated staff must take adequate precautions in storing and handling the controlled drugs, including but not limited to storage of the IP/AP in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution (Item 12).

Guidelines for supply of codeine cough preparations to a subject in any research study that is not a regulated clinical trial has been listed in Item 13.

Prescription-only medicines can only be administered to subjects by a qualified medical practitioner, or under the instructions of a qualified medical practitioner (Item 14).

If the IP/AP needs to be recalled, HSA must be notified of, and the reasons for, the intended recall immediately, but in any case no later than 24 hours before the start of the intended recall (Item 15).

7. **501-B08 Data Collection and Handling**

This SOP has been updated with the definition of “Individually-identifiable in relation to human biological material or health information pertaining to an individual” (Item 2.e) and new guidance to Data Protection according to HBRA. Information related to Data Management has been edited to be concise (Item 6).

Data Protection (Item 5)
Individuals should not attempt to re-identify anonymised information or biological material, or disclose any individually-identifiable information of a research subject except conditions listed under Item 5.1 of the SOP. Individuals receiving individually-identifiable information or human biomedical material of a research subject should not disclose any individually-identifiable information of the research subject, if at the time when the individuals receive the information or material, they knew or had reasonable grounds to believe that it had been communicated or supplied to them in a manner that breaches the HBRA or any other applicable law (Item 5.2).

8. **SOP-C01: Informed Consent Document and Process**

This SOP has been updated with the consent requirements in accordance to HPA, MA and HBRA.

The definition of Children, Legal Representative, Legally Acceptable Representative, Deputy, Donee, Donor and Specialist has been defined in this SOP (Item 2.i, 2.l, 2.m, 2.o, 2.p, 2.q, 2r).

The required and additional elements of the ICF have been updated (Item 4.1.h, 4.2.j and 4.2.k).

In accordance to HBRA, required elements of the ICF for research involving use of human removal, donation or use of human tissue has been specified in this section with respect to HBRA (Item 4.1.1).

**Persons obtaining consent:** For clinical trials regulated by HSA, only an Investigator who is a qualified practitioner is allowed to obtain informed consent from the subjects. (Item 5.5.d)

**Informed Consent Documentation:** Subject must be given a complete copy of the signed informed consent form. A complete copy of the original signed informed consent form should also be filed in the investigator file. (Item 6.1)

The study team member who conducted the informed consent discussion must personally sign and date the consent form and minimally record the protocol reference, date of informed consent, informed consent process (e.g. for use of substituted consent/ impartial witness / translator, verification of the appropriate legal representative for consent), as well as the fact that a copy was given to the subject in the subject’s medical record (if applicable). (Item 6.2)

**Research Involving Children:**
For clinical trials regulated by HSA (Item 10.1 – 10.5), the Investigator must obtained consent from:
  a) The child/ minor, if the child/ minor is below the age of 21 years who is or was married
  b) Both (i) the child AND (ii) the child’s legal representative (as specified in Item 10.1.1 in the SOP) if the child/ minor is below the age of 21 years who is not or was never married
  c) The child’s legal representative only, if the child/ minor is below the age of 21 years who is not or was never married but who lacks capacity or sufficient understanding and intelligence to give such consent

For non-therapeutic clinical trials to be conducted, it should meet the conditions outlined in Section 10.2.

**For research studies regulated under HBRA** (Item 10.6), if the minor has sufficient understanding and intelligence to understand what is proposed in the biomedical research, consent should be obtained from:
  a) Both the minor AND at least one adult parent or guardian of the minor OR
b) the child/ minor only when DSRB has waived the requirement to obtain the consent of at least one adult parent or guardian of the minor

Should the child/ minor not have sufficient understanding and intelligence to understand what is proposed in the research and there are reasonable grounds for believing that biomedical research of comparable effectiveness cannot be carried out without the participation of the class of minors to which the minor belongs, consent should be obtained from at least one parent or guardian of the minor.

Should the child/ minor lacks mental capacity and there are reasonable grounds for believing that biomedical research of comparable effectiveness cannot be carried out without the participation of the class of minors to which the minor belongs; consent should be obtained from either (i) Deputy who is authorized to give consent to the biomedical research on behalf of the minor; OR (ii) at least one adult parent or guardian of the minor.

Consent for the removal or use of human tissue from children/ minor has been specified in Section 10.6.1.

For other research studies (i.e. not regulated by HSA or under HBRA), where the prospective research subject is a minor, the investigator should obtain consent from at least one adult parent or guardian of the minor (Item 10.7).

Research involving Cognitively-Impaired Subjects:

For clinical trials regulated by HSA under MA and HPA, consent of adults who lack capacity shall not be required if:

a) The investigator who is a qualified practitioner, and another qualified practitioner who is a registered medical practitioner, who is not conducting the clinical trial certify in writing that (i) the person lacks capacity to consent to being a subject; and (ii) it is not likely that the person will regain capacity within the window period;

b) Consent has been obtained from (i) that person’s legal representative; and (ii) if the legal representative is below 21 years of age, has sufficient understanding and intelligence to give the consent; and (iii) there is a reasonable prospect that participation in the clinical trial will directly benefit that person.

A legal representative is -

- The donee or deputy appointed pursuant to or under the Mental Capacity Act in relation to the giving or refusing of consent on behalf of the adult to be a subject; or

- Where there is no donee or deputy, any of the following persons in descending order of priority:
  i. a spouse of the adult;
  ii. an adult child of the adult;
  iii. a parent or guardian of the adult;
  iv. an adult sibling of the adult;
  v. any other adult named by the adult (when the adult did not lack capacity) as someone to consult on the issue of the adult being a subject.

^subject to other conditions stated in Item 11.4.1.d

For non-therapeutic clinical trials to be conducted, it should meet the conditions outlined in Section 11.5.

For human biomedical research (in accordance with the HBRA), the appropriate consent for the adult must be obtained from the following persons:
a) where there is a donee or deputy who is authorised to give consent to the biomedical 
research on behalf of the adult 
b) where there is no donee or deputy available, any of the following persons in the order of 
priority stated: 
   i) the spouse; 
   ii) an adult son or daughter; 
   iii) either parent or a guardian; 
   iv) an adult brother or sister; 
   v) any other person named by the adult as someone to be consulted on the matter 
in question or on matters of that kind.

Consent for the removal or use of human tissue from an adult who lacks mental capacity to consent 
has been specified in Section 11.9.1 and 11.9.2.

For other research studies where the prospective research subject is an adult who lacks capacity, the 
investigator should obtain consent from the following persons in descending order of priority (Item 
11.10):
   i) the spouse; 
   ii) the adult son or daughter; 
   iii) either parent or a guardian 
   iv) an adult brother or sister 
   v) any other person named by the adult as someone to be consulted on the matter in question 
or on matters of that kind.

Research involving Emergency situations: 
For clinical trials regulated by HSA under HPA and MA, the revised regulations now require an 
investigator of the trial who is a specialist and only one specialist who is not conducting the trial to 
certify in writing, the elements stated in Item 12.10, at point of enrolment before using the person in 
the trial.

If the consent of the subject cannot be obtained and it is not feasible to obtain consent from the 
Legal Representative within the window period, then the PI must ensure that, at the earliest 
feasible opportunity (including during the window period) (Item 12.12) — 
   a) All reasonable efforts are made to contact any member of the subject’s family; and 
   b) The family member is given a full and reasonable explanation of the required elements in 
the informed consent; and 
   c) The family member does not object the subject to be or to continue to be a subject in the 
trial.

When consent is obtained from the subject, the decision by the Legal Representative or family 
member ceases to apply. If the subject is still unable to consent, but the consent of the Legal 
Representative is obtained, the decision by the family member ceases to apply (Item 12.13 and 
12.14). Where the subject has been enrolled into a trial, and where the subject / legal representative 
/ any family member objects to the subject’s continued participation in the trial, the subject should 
be immediately discontinued (Item 12.15).

For human biomedical research (in accordance with the HBRA), at the point of enrolment of each 
subject, a specialist in the specialty relating to the research and who is not involved in the research 
study as a researcher or supervisor must give written certification stated in Section 12.4, prior to 
enrolling the subject into the research study.
Subject should be informed as soon as is practicable after he or she regains capacity of his or her participation in the research and given an opportunity to withdraw from further participation in the research. Subject’s Legal Representative should be informed as soon as is practicable of the subject’s participation in the research and to be given an opportunity to request that the subject be withdrawn from further participation in the research (Item 12.5).

Where the subject has been enrolled into a study, and where the subject / legal representative / any family member objects to the subject’s continued participation in the study, the subject should be immediately discontinued (Item 12.6).

New requirement from HBRA on the consent for research or removal or use of tissue for research in case of deceased persons has been specified in Item 13.

9. **501-C05: Unanticipated Problems Involving Risks to Subjects or Others**

This SOP has been updated to clarify that PI must report unexpected serious adverse drug reactions (USADR) to HSA (Item 6.c.). The time frame for UPIRTSO reporting to DSRB has also been amended:

a) For more than minimal risk studies, all problems involving local* deaths should be reported as soon as possible, but not later than 7 calendar days after first knowledge by the investigator, regardless of causality and expectedness of the death event.

b) For no more than minimal risk studies, only problems involving local* deaths that are related or possibly related to the study should be reported as soon as possible, but not later than 7 calendar days after first knowledge by the investigator.

c) For problems which are life threatening, it should be reported as soon as possible, but not later than 7 calendar days after first knowledge by the investigator.

For a), b) and c), any additional relevant information about the death/ life threatening event should be reported within 8 calendar days of making the initial report.

d) All other problems must be reported as soon as possible but not later than 15 calendar days after first knowledge by the investigator.

For Oncology studies where (a) Most of such deaths occur when the subjects are in the treatment free follow-up phase (due to natural disease progression), (b) Unrelated to the investigational product, (c) No clinically meaningful information that allows assessment of the risk-benefit relationship of the study and (d) No significant implications on the rights and welfare of the subjects, local* death reporting requirements follow the table below:

<table>
<thead>
<tr>
<th>Local* Death Occurring within 60 days (or less) after last dose</th>
<th>Local* Death Occurring more than 60 days after last dose</th>
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<tbody>
<tr>
<td>Related (unexpected or expected) Preliminary report by PI within 7 calendar days of first knowledge</td>
<td>Related (unexpected or expected) Preliminary report by PI within 7 calendar days of first knowledge</td>
</tr>
<tr>
<td>Unrelated (expected or unexpected) Preliminary report by PI within 7 calendar days of first knowledge</td>
<td>Unrelated (expected or unexpected) Routine reporting for Annual Continuing Review</td>
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Update to PCR SOP for RQM Website dated 11 Nov 2016
The PI is required to follow up with the detailed report **within 8 calendar days** after the preliminary report.

*“Local” is defined as under an NHG institution or an institution under the oversight of NHG DSRB.

10. Singapore Good Clinical Practice (SG-GCP) will obsolete from 01 November 2016. All clinical trials regulated by Health Sciences Authority (HSA) must comply with International Conference on Harmonisation Good Clinical Practice (ICH-GCP). The following SOPs consist of changes to the references section only:

A. 501-A01: Preparing, Maintaining and Communicating Proper Conduct of Research Standard Operating Procedures
B. 501-B04: Interactions with Domain Specific Review Board
C. 501-B07: Study Conduct - Monitoring
D. 501-B08: Data Collection and Handling
E. 501-B09: Study Completion Activities
F. 501-B10: Handling Audits/ Inspections

Please refer to the SOPs for all complete updates.