No. S 000

HEALTH PRODUCTS ACT
(CHAPTER 122D)

HEALTH PRODUCTS (CLINICAL TRIALS) REGULATIONS 2015

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In exercise of the powers conferred by section 72 of the Health Products Act, the Health Sciences Authority, with the approval of the Minister for Health, makes the following Regulations:

PART 1

GENERAL

Citation and commencement

1. These Regulations may be cited as the Health Products (Clinical Trials) Regulations 2015 and come into operation on 2015.

Definitions

2.—(1) In these Regulations, unless the context otherwise requires —

"adult" means a person who —

(*a*) is at least 21 years of age; or

(*b*) is below 21 years of age, and is or was married;

"adverse drug reaction" means any untoward and unintended response in a subject to an investigational therapeutic product which is related to any dose administered to that subject;

"adverse event" means any untoward medical occurrence in a subject to whom an investigational therapeutic product has

been administered, including any occurrence which is not necessarily caused by or related to that product;

"amendment" means an amendment to —

(*a*) any term of an application for authorisation, or a notification, to conduct a clinical trial; or

(*b*) any particulars or documents (including a protocol) accompanying that application or notification;

"authorisation" means an authorisation for a clinical trial referred to in regulation 7(1)(*a*)(i);

"Authority's website" means the Authority's Internet website at http://www.hsa.gov.sg as may be updated from time to time;

"institutional review board" means an institutional review board appointed under the Human Biomedical Research Act 2015 (Act 29 of 2015);

"investigational therapeutic product" means —

(*a*) a therapeutic product; or

(*b*) a placebo,

that is to be tested or used as a reference in a clinical trial;

"investigator" means an investigator of a clinical trial;

"investigator's brochure" means a document containing a summary of the clinical and non-clinical data relating to an investigational therapeutic product relevant to the study of the product in subjects;

"minor" means a person who is below 21 years of age, and is not and was never married;

"notification" means a notification of a clinical trial referred to in regulation 7(1)(*a*)(ii);

"observational trial" means a clinical trial of one or more registered therapeutic products, where all of the following conditions are met in respect of each product:

(*a*) the product is prescribed by a qualified practitioner to a patient in the usual manner in accordance with the terms of the product registration;

(*b*) the decision to prescribe the product to the patient is clearly separated from the decision to include the patient in the trial;

(*c*) the assignment of any patient involved in the trial to a particular therapeutic strategy in which the product is used is not decided in advance by a protocol but falls within the current practice of the qualified practitioner carrying out the trial;

(*d*) no diagnostic or monitoring procedure is applied to the patient involved in the study other than any procedure that is ordinarily applied in the course of the particular therapeutic strategy referred to in paragraph (*c*);

"principal investigator" means a principal investigator of a clinical trial referred to in regulation 5(1);

"principles of good clinical practice" means the principles specified in the Schedule;

"protocol" means a document that describes the objectives, design, methodology, statistical considerations and organisation of a clinical trial;

"qualified practitioner" means —

(*a*) a registered medical practitioner under the Medical Registration Act (Cap. 174); or

(*b*) a registered dentist under the Dental Registration Act (Cap. 76) whose name appears in the first division of the Register of Dentists maintained and kept under section 13(1)(*a*) of that Act;

"relevant institutional review board", in relation to a clinical trial, means the institutional review board that approved the trial;

"serious adverse drug reaction" means any adverse drug reaction which —

(*a*) results in death;

(*b*) is life-threatening;

(*c*) requires in-patient hospitalisation or prolongation of existing hospitalisation;

(*d*) results in persistent or significant disability or incapacity; or

(*e*) consists of a congenital anomaly or birth defect;

"serious adverse event" means any adverse event that —

(*a*) results in death;

(*b*) is life-threatening;

(*c*) requires in-patient hospitalisation or prolongation of existing hospitalisation;

(*d*) results in persistent or significant disability or incapacity; or

(*e*) consists of a congenital anomaly or birth defect;

"sponsor", in relation to a clinical trial, means a person who takes responsibility for the initiation, management or financing of the clinical trial;

"subject", in relation to a clinical trial, means a person, whether or not a patient, who participates in the trial —

(*a*) as a recipient of an investigational therapeutic product to which the trial relates, or of some other treatment or procedure in that trial; or

(*b*) as a control, without receiving any such investigational therapeutic product, or any such treatment or procedure;

"substantial amendment", in relation to a clinical trial, means an amendment —

(*a*) which changes a sponsor or principal investigator of the trial; or

(*b*) which is likely to affect to a significant degree —

(i) the safety, or physical or mental integrity, of any subject of the trial;

(ii) the scientific value of the trial;

(iii) the conduct or management of the trial; or

(iv) the quality or safety of any investigational therapeutic product used in the trial;

"therapeutic product" means a therapeutic product as defined in the First Schedule to the Act, whether registered or unregistered under the Act;

"trial site" means a place where activities relating to a clinical trial are conducted;

"unexpected serious adverse drug reaction" or "USADR" means a serious adverse drug reaction, the nature and severity of which is not consistent with the information about the investigational therapeutic product in question set out —

(*a*) in the case of an investigational therapeutic product that is a registered health product, in the product information leaflet or the investigator's brochure relating to the product; and

(*b*) in the case of an investigational therapeutic product that is not a registered health product, in the investigator's brochure relating to the product;

"window period" means the period, determined based on scientific evidence, within which an investigational therapeutic product must be administered to a subject in a clinical trial for it to have the intended potential direct benefit to the subject.

(2) For the purposes of these Regulations —

(*a*) a reference to a person who lacks capacity to consent to the person or another person being a subject in a clinical trial, is a reference to a person who lacks capacity to so consent within the meaning of section 4 of the Mental Capacity Act (Cap. 177A); and

(*b*) a reference to a person who has such capacity is a reference to a person who does not lack such capacity.

(3) A reference in these Regulations to a legal representative of a subject or a prospective subject of a clinical trial, is a reference to a person having capacity who is —

(*a*) where the subject or prospective subject is a minor —

(i) a deputy appointed under the Mental Capacity Act in relation to the giving or refusing of consent on behalf of the minor to being a subject in clinical trials; or

(ii) if there is no deputy referred to in sub-paragraph (i), the adult parent, or (if there is no adult parent to act, or who is entitled to act as a legal representative of the minor) guardian, of the minor; and

(*b*) where the subject or prospective subject is an adult —

(i) 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 participate in clinical trials; or

(ii) where there is no donee or deputy referred to in sub-paragraph (i), subject to paragraph (4), any of the following persons in descending order of priority:

(A) a spouse of the adult;

(B) an adult child of the adult;

(C) a parent or guardian of the adult;

(D) an adult sibling of the adult;

(E) any other adult named by the adult (when the adult did not lack capacity) as someone to consult on the issue of the adult participating in clinical trials;

(4) For the purpose of paragraph (3)(*b*)(ii), all of the following apply:

(*a*) the order of priority applies in the absence of actual notice of any contrary indication given by the subject or prospective subject (when the subject or prospective subject did not lack capacity);

(*b*) a person referred to in that paragraph cannot be a legal representative of the subject or prospective subject if the person is also a donee or deputy and there is an express provision in the lasting power of attorney or appointment by

the court that the donee or deputy is not authorised to give consent to the subject or prospective subject being a subject in the clinical trial;

(*c*) a person referred to in paragraph (3)(*b*)(ii)(B), (C), (D) or (E) —

(i) may be a legal representative only if all persons having a higher priority compared to that person are not available or cannot be a legal representative by reason of sub-paragraph (*a*) or (*b*); and

(ii) cannot be a legal representative if any person having an equal or a higher priority compared to that person (other than a person who cannot be a legal representative by reason of sub-paragraph (*a*) or (*b*)) has objected to the subject or prospective subject being a subject in the clinical trial.

Application of Regulations to clinical trials of therapeutic products

3. These Regulations apply to all clinical trials of therapeutic products that are not observational trials.

PART 2

CLINICAL TRIALS OF THERAPEUTIC PRODUCTS

Division 1 — General

Sponsors

4.—(1) Every clinical trial must have one, and only one sponsor.

(2) Despite paragraph (1), the Authority may, in its discretion, allow more than one sponsor for a clinical trial in circumstances where all the sponsors of the trial appoint a lead sponsor from amongst themselves.

(3) For a trial referred to in paragraph (2) —

(*a*) an obligation of the sponsor in regulations 6, 8(1), 9(1), 10(4) and (6), 11(1) and (3), 12, 25(1)(*a*)(ii) and (2)(*b*) is an obligation of the lead sponsor of the trial; and

(*b*) an obligation of the sponsor in any other provision of these Regulations is an obligation of each of the sponsors of the trial in relation to the part of the trial for which the sponsor has assumed responsibilities as sponsor (unless the provision specifies otherwise) and a reference to the clinical trial in that provision is to that part of the trial.

(4) Without prejudice to paragraph (3) —

(*a*) the sponsor, or in a clinical trial with more than one sponsor, the lead sponsor, must —

(i) evaluate during the trial on an on-going basis the safety of the investigational therapeutic product; and

(ii) promptly notify all principal investigators of the trial and, in a clinical trial with more than one sponsor, all other sponsors and all principal investigators of the trial, of —

(A) any information which suggests that the safety of the subjects of the trial could be adversely affected (including of any USADR occurring in any subject of the trial); and

(B) any findings which could impact the conduct of the trial; and

(*b*) in a clinical trial with more than one sponsor, every sponsor that is not a lead sponsor must —

(i) promptly report to the lead sponsor any serious adverse event which occurs in a subject during the trial, and furnish to the lead sponsor a detailed written report on the event as soon as possible thereafter, other than any serious adverse event specified in the protocol as not requiring immediate reporting;

(ii) promptly report to the lead sponsor any information which suggests that the safety of any subject of the trial could be adversely affected;

(iii) promptly report to the lead sponsor any findings which could impact the conduct of the trial; and

(iv) provide such information to the lead sponsor as may be necessary for the lead sponsor to comply with regulations 6, 8(1), 9(1), 10(4) and (6), 11(1) and (3), 12, 25(1)(*a*)(ii) and (2)(*b*) in relation to the trial.

(5) The sponsor may delegate all or any of the sponsor's functions under these Regulations to any person, but any such arrangement does not affect the responsibility of the sponsor.

(6) The sponsor and a person to whom the sponsor has delegated the sponsor's functions under paragraph (5) must each carry out their respective functions in accordance with the principles of good clinical practice.

Principal investigator, etc.

5.—(1) The sponsor must ensure that the clinical trial is conducted by or under the supervision of a principal investigator who —

(*a*) is a qualified practitioner; and

(*b*) is qualified by training and experience, and has adequate resources, to properly conduct the trial.

(2) The principal investigator must declare to the institutional review board whose approval for the clinical trial is being sought, every financial interest which the principal investigator, and any person assisting the principal investigator in the trial, directly or indirectly, has in the trial.

(3) The principal investigator must ensure that —

(*a*) the medical care given to a subject in the trial, and all medical decisions relating to the clinical trial made on behalf of the subject, is the responsibility of at least one investigator who is a qualified practitioner referred to in paragraph (*a*) of the definition of "qualified practitioner" in regulation 2(1); and

(*b*) the dental care given to a subject in the trial, and all dental decisions relating to the clinical trial made on behalf of the subject, is the responsibility of at least one investigator who is a qualified practitioner referred to in paragraph (*b*) of the definition of "qualified practitioner" in regulation 2(1).

(4) Only an investigator who is a qualified practitioner, and any person assisting the investigator in the clinical trial, may treat or administer any investigational therapeutic product of the trial to a subject of the trial.

(5) Despite paragraph (4), in an emergency, any qualified practitioner may treat a subject if it is in the interest of the subject.

(6) The principal investigator and any person assisting the principal investigator must conduct the clinical trial in accordance with these Regulations.

Investigator's brochure

6. The sponsor of a proposed clinical trial must ensure that the investigator's brochure for the trial —

(*a*) presents the information it contains in a concise, simple, objective, balanced and non-promotional form that enables a clinician or potential investigator to understand it and make an unbiased risk-benefit assessment of the appropriateness of the trial; and

(*b*) is kept up-to-date.

Division 2 — Regulatory submissions for clinical trials of therapeutic products

Requirement for authorisation for or notification of clinical trial

7.—(1) The Authority must specify on the Authority's website —

(*a*) the clinical trials that require its authorisation; and

(*b*) the clinical trials which, because the trials only involve the use of any therapeutic product that is a registered health product and pose no, or minimal, additional risk to the safety of subjects compared to normal clinical practice, need only be notified to it.

(2) A person must not commence or conduct a clinical trial unless —

(*a*) either —

(i) if the trial is one that must be authorised by the Authority, it has been so authorised in accordance with regulation 8; or

(ii) if the trial need only be notified to the Authority, it has been so notified and confirmation of the Authority's acceptance of the notification has been received, in accordance with regulation 9; and

(*b*) the conduct of the trial has been approved by an institutional review board.

Application for authorisation for clinical trial

8.—(1) The sponsor must obtain authorisation by the Authority for the clinical trial under regulation 7(1)(*a*)(i) before the commencement of the trial.

(2) The application for authorisation must be made in the form and manner specified on the Authority's website.

(3) The Authority may authorise a clinical trial subject to such conditions as the Authority thinks necessary and may, from time to time, by notice in writing to the person granted the authorisation —

(*a*) modify or remove any condition of the authorisation; or

(*b*) attach any new condition to the authorisation.

(4) The conditions referred to in paragraph (3) may include a condition requiring the sponsor to obtain and maintain insurance to provide compensation in the event of injury or loss arising from the trial on such terms as the Authority may approve.

(5) The Authority may refuse to authorise, or suspend or revoke any authorisation, of a clinical trial.

(6) Any person aggrieved by a refusal, suspension or revocation referred to in paragraph (5) may appeal to the Minister, whose decision is final.

Notification of clinical trial

9.—(1) The sponsor must notify the Authority of the clinical trial under regulation 7(1)(*a*)(ii), and receive the Authority's acceptance of the notification, before commencement of the trial.

(2) The notification must be made in the form and manner specified on the Authority's website.

(3) The Authority may accept the notification subject to such conditions as the Authority thinks necessary and may, from time to time, by notice in writing to the person granted the notification —

(*a*) modify or remove any condition of the notification; or

(*b*) attach any new condition to the notification.

(4) The conditions referred to in paragraph (3) may include a condition requiring the sponsor of the trial to obtain and maintain insurance to provide compensation in the event of injury or loss arising from the trial on such terms as the Authority may approve.

Amendments and substantial amendments to clinical trial, etc.

10.—(1) The Authority may, at any time, make an amendment (including a substantial amendment) if it appears to the Authority that the amendment is necessary to ensure —

(*a*) the safety or scientific validity of the clinical trial;

(*b*) compliance with the principles of good clinical practice in relation to the trial; or

(*c*) compliance with the conditions of the Authority's authorisation or acceptance of notification.

(2) Subject to regulation 21, in the case of a clinical trial that has been authorised by the Authority under regulation 8, the sponsor must not make a substantial amendment, except with the approval of the Authority.

(3) An application for approval of a substantial amendment referred to in paragraph (2) must be made by the sponsor in the form and manner specified on the Authority's website.

(4) Subject to regulation 21, in the case of a clinical trial that has been notified to the Authority under regulation 9, the sponsor must not make a substantial amendment until the substantial amendment has been notified to the Authority and the sponsor has received confirmation of the Authority's acceptance of the notification.

(5) A notification of a substantial amendment referred to in paragraph (4) must be made by the sponsor in the form and manner specified on the Authority's website.

(6) The sponsor must —

(*a*) keep records of all amendments; and

(*b*) send such records, or copies of such records, to the Authority, in accordance with any request by the Authority for the same.

Notification of serious breaches and urgent safety measures

11.—(1) The sponsor of a clinical trial must notify the Authority in writing of any serious breach during the clinical trial of any of the following, within 7 days after becoming aware of the breach:

(*a*) the principles of good clinical practice;

(*b*) the protocol relating to the trial, as amended from time to time in accordance with regulation 10;

(*c*) these Regulations.

(2) Where the relevant institutional review board requires any person to report to it any serious breach of any of the following during a clinical trial, the person must do so in accordance with the requirements of the board:

(*a*) the principles of good clinical practice;

(*b*) the protocol relating to the trial, as amended from time to time in accordance with regulation 10.

(3) The sponsor of a clinical trial must immediately, and in any event no later than 3 days after the date any urgent safety measures referred to in regulation 21 are taken in relation to a subject of the clinical trial, give written notice to the Authority of the measures taken and the circumstances giving rise to those measures.

(4) In this regulation, "serious breach" means a breach during a clinical trial which is likely to affect to a significant degree —

(*a*) the safety, or physical or mental integrity, of any subject of the trial; or

(*b*) the scientific value of the trial.

Conclusion of clinical trial, etc.

12.—(1) The sponsor must —

(*a*) subject to paragraph (2), notify the Authority of the conclusion of the clinical trial within 30 days after the date of such conclusion; and

(*b*) submit to the Authority a final report of the trial within 90 days after the date of such conclusion, or such longer period as the Authority may allow in any particular case.

(2) The sponsor must notify the Authority of any suspension of the clinical trial, or its termination (if the termination takes place before the date of conclusion of the trial or the concluding event specified in the protocol for the trial), within 15 days after the date of the suspension or termination.

(3) The notifications referred to in paragraphs (1) and (2) must be in the form and manner required by the Authority.

Division 3 — General duties

Subdivision (1) — Good clinical practice and conduct of clinical trials

Conduct of clinical trials: good clinical practice

13.—(1) Every person conducting a clinical trial must do so in accordance with the principles of good clinical practice.

(2) The sponsor must put and keep in place arrangements for the purpose of ensuring that the principles of good clinical practice are satisfied or adhered to by all persons involved in conducting the trial.

Conduct of clinical trials: in accordance with authorisations and notifications

14. Subject to regulation 21, every person conducting a clinical trial must do so in accordance with —

(*a*) the protocol relating to the trial; and

(*b*) the conditions of the authorisation or acceptance of notification, as the case may be, relating to the trial,

as may be amended from time to time in accordance with regulation 10.

Place of clinical trial

15. The sponsor and principal investigator must ensure that the clinical trial is conducted only at such trial site as may be specified in the authorisation for or notification of the trial, as the case may be.

Subdivision (2) — Duties relating to consents and provision of information

Consent of subjects, etc., in clinical trials

16.—(1) The principal investigator of a clinical trial must ensure that no person is used as a subject in the trial except in accordance with this regulation and regulations 17 to 20, as may be applicable.

(2) Subject to paragraph (3), an adult must not be a subject in a clinical trial unless, before the adult becomes a subject in the trial, the adult consents to being one.

(3) Despite paragraph (2), where an investigator of the trial who is a qualified practitioner, and another qualified practitioner who is a registered medical practitioner under the Medical Registration Act (Cap. 174) who is not conducting the clinical trial, certify in writing that —

(*a*) the adult lacks capacity to consent to being a subject in the trial; and

(*b*) it is not likely that the adult will regain capacity within the window period,

then, the consent of the adult need not be obtained if the conditions in paragraph (4) are met.

(4) For the purposes of paragraph (3), the conditions are all of the following:

(*a*) the adult's legal representative —

(i) consents to the adult being such a subject; and

(ii) if the legal representative is below 21 years of age, has sufficient understanding and intelligence to give the consent;

(*b*) it is established that there is a reasonable prospect that participation in the trial will directly benefit the adult, unless —

(i) the objectives of the trial cannot be met by means of a trial in subjects who can give consent personally;

(ii) the trial is conducted in subjects having a disease or condition for which the therapeutic product being tested in the trial is intended;

(iii) there is some direct benefit for the group of subjects involved in the trial;

(iv) the foreseeable risks to the subjects involved in the trial are low; and

(v) the negative impact on the well-being of subjects involved in the trial is minimised and low.

(5) Subject to paragraph (6), a minor must not be a subject in a clinical trial unless, before the minor becomes a subject in the trial —

(*a*) the minor and the minor's legal representative consent to the minor being such a subject; and

(*b*) if the legal representative is below the age of 21 years, the legal representative has sufficient understanding and intelligence to give the consent.

(6) Despite paragraph (5), where the minor lacks capacity to give consent to being a subject in a clinical trial, or the minor lacks sufficient understanding and intelligence to give such consent, then, the consent of the minor need not be obtained if the conditions in paragraph (7) are met.

(7) For the purposes of paragraph (6), the conditions are all of the following:

(*a*) the minor's legal representative —

(i) consents to the minor being such a subject; and

(ii) if the legal representative is below the age of 21 years, has sufficient understanding and intelligence to give the consent;

(*b*) it is established that there is a reasonable prospect that participation in the trial will directly benefit the minor, unless —

(i) the objectives of the trial cannot be met by means of a trial in subjects who can give consent personally;

(ii) the trial is conducted in subjects having a disease or condition for which the therapeutic product being tested in the trial is intended;

(iii) there is some direct benefit for the group of subjects involved in the trial;

(iv) the foreseeable risks to the subjects involved in the trial are low; and

(v) the negative impact on the well-being of subjects involved in the trial is minimised and low.

(8) For the purposes of paragraphs (4)(*b*) and (7)(*b*), participation in a clinical trial does not have any reasonable prospect of direct benefit to a person unless —

(*a*) appropriate non-clinical and clinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the proposed use of the therapeutic product to provide a direct benefit to the person; and

(*b*) the risks associated with the clinical trial are reasonable in relation to what is known about —

(i) the medical condition of the person;

(ii) the risks and benefits of standard therapy, if any; and

(iii) the risks and benefits of the proposed use of the therapeutic product.

Consent of subjects, etc., in clinical trials in emergency situations

17.—(1) For the purposes of this regulation, a clinical trial in an emergency situation is a clinical trial to determine the safety or efficacy of the therapeutic product being tested in the trial on subjects where —

(*a*) the subjects are facing a life-threatening situation that necessitates intervention;

(*b*) the subjects are unable to consent to being subjects in the trial as a result of their medical condition; and

(*c*) it is not feasible to request consents from the legal representatives of the subjects within the window period.

(2) A person must not commence or conduct a clinical trial in an emergency situation unless —

(*a*) the trial has been, in accordance with regulation 7 and paragraph (4) —

(i) authorised by the Authority; or

(ii) notified to the Authority and confirmation of the Authority's acceptance of the notification has been received;

(*b*) an institutional review board has approved the conduct of the trial in accordance with paragraph (6)(*b*).

(3) A person must not commence or conduct a clinical trial in an emergency situation except in accordance with the conditions in paragraph (5).

(4) For the purposes of paragraph (2), the Authority must not give an authorisation or accept a notification of a clinical trial in an emergency situation unless the principal investigator and 2 specialists who are not conducting the trial certify in writing that —

(*a*) the trial needs to be conducted on potential subjects who are facing a life-threatening situation to determine the safety or efficacy of a therapeutic product;

(*b*) available treatments or procedures are unproven or unsatisfactory;

(*c*) there is a reasonable prospect that participation in the trial will directly benefit the potential subjects because —

(i) the potential subjects are facing a life-threatening situation that necessitates intervention;

(ii) the appropriate non-clinical and clinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the proposed use of the therapeutic product to provide a direct benefit to the potential subjects; and

(iii) the risks associated with the trial are reasonable in relation to what is known about —

(A) the medical condition of the potential subjects;

(B) the risks and benefits of standard therapy, if any; and

(C) the risks and benefits of the proposed use of the therapeutic product;

(*d*) the potential subjects are unable to consent to being subjects as a result of their medical condition;

(*e*) it is not feasible to obtain consent from the legal representatives of the potential subjects within the window period;

(*f*) there is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the trial; and

(*g*) the trial cannot practicably be carried out if the consents referred to in regulation 16 must be obtained.

(5) The Authority may give an authorisation or accept a notification for a clinical trial in an emergency situation, subject to such conditions as the Authority may think fit to impose.

(6) The consents referred to in regulation 16 need not be obtained in order for a person to be used as a subject in a clinical trial in an emergency situation if all of the following are satisfied:

(*a*) the Authority has authorised or accepted a notification of the trial;

(*b*) the relevant institutional review board has reviewed and approved —

(i) the circumstances in which the consents referred to in regulation 16 need not be obtained for the purposes of the trial; and

(ii) the procedure for informing the person, the legal representative or family member, as the case may be, of the person at the earliest feasible opportunity, of the person's participation in the trial, and the right to discontinue the person's participation at any time without penalty, in accordance with paragraphs (8) to (11);

(*c*) the principal investigator and one specialist who is not conducting the trial certify in writing before using the person in the trial that —

(i) the person is facing a life-threatening situation which necessitates intervention;

(ii) the person is unable to consent as a result of the person's medical condition;

(iii) it is not feasible to obtain consent from the legal representative of the person within the window period; and

(iv) neither the person nor the legal representative of the person nor any member of the person's family has informed the principal investigator of any objection to the person being a subject in the clinical trial.

(7) Although the consents referred to in regulation 16 need not be obtained in relation to a clinical trial in an emergency situation, paragraphs (8) to (11) must be complied with.

(8) If, at any time in a clinical trial in an emergency situation, a person referred to in paragraph (6) who is about to be or is used as a subject in the trial regains capacity to give consent, the principal investigator must ensure that, at the earliest feasible opportunity —

(*a*) the person is given a full and reasonable explanation of the matters referred to in regulation 19(1); and

(*b*) the consent of the person to continue to be a subject in the trial is obtained.

(9) If a person referred to in paragraph (6) is a subject in a clinical trial in an emergency situation and the consent of the person to be a subject cannot be obtained because of the medical condition of the person, the principal investigator must ensure that, at the earliest feasible opportunity —

(*a*) all reasonable efforts are made to contact the legal representative of the person;

(*b*) the legal representative is given a full and reasonable explanation of the matters referred to in regulation 19(1)(*a*) to (*u*); and

(*c*) the legal representative's consent for the person to continue to be a subject in the clinical trial is obtained.

(10) Where it is unlikely that paragraph (9) can be complied with, then the principal investigator must ensure that, at the earliest feasible opportunity —

(*a*) all reasonable efforts are made to contact any member of the person's family; and

(*b*) the member of the person's family is given a full and reasonable explanation of the matters referred to in regulation 19(1)(*a*) to (*u*).

(11) The principal investigator must ensure that a person ceases to be a subject in a clinical trial if —

(*a*) the person or the legal representative of the person refuses to give the consent referred to in paragraph (8) or (9), as the case may be; or

(*b*) where neither the consent of the person nor the consent of the legal representative of the person has been obtained, any member of the person's family informs the principal investigator of any objection to the person being a subject in the trial.

(12) In this regulation, "specialist" means a person registered as a specialist under section 22 of the Medical Registration Act (Cap. 174) in the branch of medicine under which the subject is to be treated.

General requirements as to consent

18.—(1) Any consent required under these Regulations for a person to be a subject in a clinical trial must be obtained by an investigator who is a qualified practitioner in accordance with this regulation.

(2) The consent must be —

(*a*) in writing and in the form approved by both the Authority and the relevant institutional review board; and

(*b*) signed and dated by the person giving the consent.

(3) If the person giving the consent is unable to sign or date the written form referred to in paragraph (2)(*a*), the consent must —

(*a*) be signified and dated in the form and manner approved by the relevant institutional review board; and

(*b*) be obtained in the presence of an impartial witness.

(4) If the person giving the consent is unable to read, the written form referred to in paragraph (2)(*a*) must be read and explained to the person in the presence of an impartial witness.

(5) The impartial witness referred to in paragraph (3) or (4), as the case may be, must sign and date the written form referred to in paragraph (2)(*a*) to attest that —

(*a*) in the case of paragraph (4), the written form was accurately explained to the person giving the consent; and

(*b*) in any case, the person's consent was freely given.

(6) Any legal representative making a decision for the purposes of regulation 16 or 17, or a family member making a decision for the purpose of regulation 17(10)(*c*), must act in the best interests of the person to be used as a subject in the clinical trial.

(7) Section 6 of the Mental Capacity Act (Cap. 177A) applies for the purpose of determining what is in the best interests of a subject in a clinical trial.

(8) Where consent for a person to participate as a subject in a clinical trial is obtained in accordance with these Regulations, or is not required under these Regulations, then the consent is validly obtained or waived, as the case may be, despite any other requirement in any other written law or rule of law.

Duty to give full explanation and information

19.—(1) Before a potential subject participates in a clinical trial, the principal investigator must ensure that a full and reasonable explanation of all of the following is given to the person whose consent is required under these Regulations in order for the potential subject to participate in the trial (being the potential subject, the legal representative of the potential subject, or the potential subject and such legal representative, as the case may be):

(*a*) that the trial involves research;

(*b*) the purpose of the trial;

(*c*) the treatments or procedures to be administered in the trial and the probability for random assignment of each treatment or procedure;

(*d*) the procedures to be followed in the trial, including all invasive procedures;

(*e*) the responsibilities of the subject;

(*f*) the aspects of the trial which are experimental;

(*g*) the reasonably foreseeable risks or inconveniences to the subject and, where applicable, to any embryo, foetus or nursing infant;

(*h*) the reasonably expected benefits, including whether there is any intended clinical benefit to the subject;

(*i*) any alternative procedures or treatments available to the subject, and their potential benefits and risks;

(*j*) any compensation and treatment available to the subject in the event of injury arising from participation in the trial;

(*k*) the circumstances which may result in the pro-ration of payment to the subject for participating in the trial;

(*l*) any anticipated expenses to the subject from participating in the trial;

(*m*) that the subject's participation in the trial is voluntary and that the subject's participation in the trial may be refused, or the subject withdrawn from the trial, at any time without penalty or loss of benefits which the subject would be entitled;

(*n*) the persons who will be granted access to the subject's medical records and the extent of such access, including the possibility that the Authority may inspect the records;

(*o*) the extent to which records identifying the subject will be kept confidential;

(*p*) that any person whose consent is required under regulation 16 (including a subject referred to in regulation 16(3) to whom paragraph (3) applies) will be informed in a timely manner of any information which becomes available and which may be relevant to the decision of the person to continue, or to allow the subject to continue (as the case may be) participating in the trial as a subject;

(*q*) the persons to contact for further information relating to the trial and the rights of subjects in the event of injury arising from participation in the trial;

(*r*) any foreseeable circumstances under or reasons for which a subject's participation may be terminated;

(*s*) the expected duration of the subject's participation in the trial;

(*t*) the approximate number of subjects involved in the trial;

(*u*) any other information which the Authority may require to be given.

(2) If any information becomes available which may be relevant to the decision of a subject, or of a legal representative to allow a subject, to continue participating in a clinical trial, the principal investigator must ensure that, at the earliest feasible opportunity, a full and reasonable explanation of that information is given to the person whose consent is required in order for the subject to continue participating in the trial (being the subject (including a subject referred to in regulation 16(3) to whom paragraph (3) applies), the legal representative of the subject, or the subject and such legal representative, as the case may be).

(3) If the subject used in a clinical trial is a person referred to in regulation 16(3) and the person subsequently regains capacity to consent to being a subject in the trial, the principal investigator must ensure that, at the earliest feasible opportunity —

(*a*) the person is given a full and reasonable explanation of the matters referred to in paragraph (1); and

(*b*) the person's consent to continue being a subject in the trial is obtained.

(4) If the person referred to in paragraph (3) refuses to consent, the principal investigator must ensure that the person ceases to be used as a subject in the clinical trial.

(5) The principal investigator must ensure that the explanations referred to in paragraph (1), (2) or (3), as the case may be, are given by the principal investigator, another investigator involved in the clinical trial, or a person authorised by the principal investigator.

Coercion

20. A person must not, by means of any coercion, intimidation, deception or misrepresentation, cause, compel or induce another person —

(*a*) to be, or continue to be, a subject in a clinical trial; or

(*b*) to give consent, or refrain from withdrawing consent, for the purposes of a trial.

Subdivision (3) — Duties relating to safety and interests of subjects

Urgent safety measures

21. In order to protect any subject of a clinical trial against any immediate hazard to the health or safety of the subject, the sponsor and any investigator may take appropriate urgent safety measures.

Suspension or termination of clinical trial

22.—(1) The Authority may require the suspension or termination of a clinical trial, or any part of a clinical trial, authorised by or notified to it, or the suspension or termination of the conduct of such a trial at a particular trial site, if, or if the Authority has reasonable grounds to suspect that —

(*a*) any information provided in respect of the application for authorisation or the notification of the trial is false or misleading;

(*b*) any sponsor, principal investigator or person assisting the principal investigator has contravened, is contravening or is likely to contravene —

(i) any condition to which the authorisation or acceptance of notification of the trial is subject; or

(ii) any provision of these Regulations;

(*c*) any ground for the conduct of the trial on the basis of scientific validity is no longer applicable or true; or

(*d*) the continuance of the trial will compromise the safety of any subject of the trial.

(2) Where the Authority has suspended or terminated a clinical trial, the sponsor and principal investigator must ensure that the suspension or termination is adhered to by all persons involved in the trial.

Subdivision (4) — Duties relating to information obtained and reports

Record of clinical trials

23.—(1) The sponsor and principal investigator must keep such records of the clinical trial, in accordance with paragraph (2), as will individually and collectively —

(*a*) permit proper evaluations to be made of the conduct of the trial and the quality of the data produced; and

(*b*) demonstrate compliance by each person involved in the trial with the principles of good clinical practice and all applicable regulatory requirements.

(2) The records referred to in paragraph (1) must —

(*a*) be kept up-to-date at all times;

(*b*) be available at all times for inspection by the Authority or any person authorised by the Authority in that behalf; and

(*c*) be kept at least until the later or the latest, as the case may be, of the following:

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

(ii) the expiry of 2 years after the last of such registrations is granted;

(iii) where the clinical trial is terminated, the expiry of 2 years after the Authority has been informed of the termination of the clinical trial under regulation 12;

(iv) the expiry of 6 years after the conclusion of the clinical trial;

(v) the expiry of such other period as the Authority may direct in any particular case.

(3) Without limiting the generality of paragraph (1), the principal investigator must maintain a record of every person assisting the

principal investigator in the clinical trial, containing all of the following information:

(*a*) the person's name;

(*b*) the person's qualifications;

(*c*) the person's responsibilities in the trial.

Division 4 — Vigilance

Notifications of serious adverse events

24.—(1) A principal investigator of any part of a clinical trial must immediately report any serious adverse event which occurs in a subject during the part of the trial, to the sponsor who has assumed responsibilities as sponsor for the part of the trial.

(2) As soon as possible after making the report referred to in paragraph (1), the principal investigator must furnish to the sponsor a detailed written report on the event.

(3) Paragraph (1) does not apply to any serious adverse event specified in the protocol or investigator's brochure for the clinical trial as not requiring immediate reporting.

(4) Where the relevant institutional review board requires any matter referred to in paragraph (1) to be reported to it, the person required by the board to do so must make the report to the board in accordance with the requirements of the board.

Notifications of unexpected serious adverse drug reactions

25.—(1) Where any USADR occurs in a subject during the clinical trial which results in death or is life-threatening, the sponsor must ensure that —

(*a*) all relevant information about the reaction is —

(i) recorded; and

(ii) reported to the Authority as soon as possible and in any event not later than 7 days after the sponsor first becomes aware of the event; and

(*b*) any additional relevant information about the USADR is —

(i) recorded; and

(ii) sent to the Authority within 8 days of making the record referred to in sub-paragraph (i).

(2) Where any USADR occurs in a subject during the clinical trial, other than a USADR referred to in paragraph (1), the sponsor must ensure that all relevant information about the reaction is —

(*a*) recorded; and

(*b*) reported to the Authority as soon as possible and in any event not later than 15 days after the sponsor first becomes aware of the event.

Division 5 — Labelling

Investigational therapeutic product and auxiliary therapeutic product labelling

26.—(1) The sponsor must ensure that every investigational therapeutic product and every auxiliary therapeutic product used in the clinical trial is labelled with such information as may be required by the Authority for all of the following purposes:

(*a*) to ensure protection of the subject and traceability;

(*b*) to enable identification of the product and the trial;

(*c*) to facilitate proper use and storage of the product;

(*d*) to ensure the reliability and robustness of data generated in the trial.

(2) Without limiting the generality of paragraph (1) and subject to paragraphs (4), (5) and (6), the sponsor must ensure that every investigational therapeutic product, and every unregistered auxiliary therapeutic product, used in the clinical trial is labelled with all of the following information in accordance with paragraph (3):

(*a*) the name, address and telephone number of the main contact for —

(i) information on the product;

(ii) information on the trial; and

(iii) emergency unblinding;

(*b*) the name of the substance used in the therapeutic product and its strength or potency, as well as, in the case of blinded trials, the name of the comparator or placebo;

(*c*) the pharmaceutical form, route of administration and quantity of dosage units of the product;

(*d*) the batch or code number identifying the contents and packaging operation of the product;

(*e*) a clinical trial reference code allowing identification of the trial, site, investigator and sponsor;

(*f*) the trial subject identification number or treatment number and, where relevant, visit number;

(*g*) the directions for use of the product (which may be a reference to a leaflet or other explanatory document intended for use by the subject or person administering the product);

(*h*) the words "For clinical trial use" or similar wordings;

(*i*) the storage conditions;

(*j*) the period of use (which may be an expiry date or a re-test date), in month and year format and in a manner that avoids any confusion as to which is the month and which is the year.

(3) The information referred to in paragraph (2) must be in English, and must be clearly legible and unambiguous.

(4) The address and telephone number referred to in paragraph (2)(*a*) need not appear on the label if the subjects are given a leaflet or card providing such information and instructed to keep the leaflet or card in their possession at all times.

(5) The information referred to in paragraph (2)(*a*), (*c*) to (*f*), (*g*) and (*j*) need not appear on the label if they are available by any other means, so long as —

(*a*) paragraph (1) is complied with; and

(*b*) the reasons for the omission are set out in the protocol or such other document as the Authority may allow.

(6) Where a registered investigational therapeutic product satisfies the requirements of paragraph (9), the information referred to in paragraph (2), other than the information referred to in sub-paragraphs (*e*) and (*h*) of that paragraph, need not appear on the label.

(7) For the purpose of paragraph (6), the information referred to in paragraph (2)(*e*) must appear on the label even if it appears elsewhere.

(8) For the purpose of paragraph (6), the information to appear on the label must not obscure the labelling required under the Health Products (Therapeutic Products) Regulations 2015 (G.N. No. S XX/2015).

(9) The requirements for the purpose of paragraph (6) are as follows:

(*a*) the registered investigational therapeutic product is not used in the clinical trial in a blinded fashion;

(*b*) the registered investigational therapeutic product is not re-packaged for use in the trial;

(*c*) the registered investigational therapeutic product is used in accordance with the terms of its product registration;

(*d*) the registered investigational therapeutic product is labelled in accordance with the Health Products (Therapeutic Products) Regulations 2015.

(10) In this regulation, "auxiliary therapeutic product" means a therapeutic product used for the needs of a clinical trial as described in the protocol, but not as an investigational therapeutic product.

PART 3

MISCELLANEOUS

Protection of confidential information

27.—(1) For the purposes of section 66(2)(*d*) of the Act, the Authority may —

(*a*) disclose confidential information relating to an investigational health product —

(i) for any purpose with the consent of the person who applied for authorisation for, or notified the Authority of, the clinical trial to which the information relates; or

(ii) as the Authority considers necessary to protect the health or safety of members of the public; or

(*b*) disclose confidential information relating to an investigational health product to a Government department or statutory body for the purposes of the Government department or statutory body if, in the opinion of the Authority, the Government department or statutory body, as the case may be, will take reasonable steps to ensure the information is kept confidential.

(2) The power to grant consent under paragraph (1)(*a*)(i) may be exercised by a person other than the person referred to in that paragraph if —

(*a*) the person referred to in paragraph (1)(*a*)(i) —

(i) has notified the Authority in writing that the other person may grant the consent; and

(ii) has not notified the Authority in writing that the other person's authority to grant the consent has been withdrawn; or

(*b*) the rights of the person referred to in paragraph (1)(*a*)(i) in respect of the relevant confidential information have been transferred to the other person, and the person or the other person has notified the Authority in writing of the transfer.

Publication of information on clinical trials

28. For the purposes of section 66(2)(*d*) of the Act, the Authority may from time to time, for the information of the public, publish in a clinical trial register such particulars of any application for authorisation or a notification which it receives in such manner as it may determine.

PART 4

PENALTIES

Penalty

29. Any person who contravenes regulation 4(4) [and (6)?], 5(1), (2), (3), (4) or (6), 6, 7(1), 8(1), 9(1), 10(3), (5) or (7), 11(1), (2) or (3), 12(1) or (2), 13(1) or (2), 14, 15, 16(1), 17(2), (8), (9), (10) or (11), 18(1) or (6), 19(1), (2), (3), (4) or (5), 20, 22(2), 23(1) or (3), 24(1), (2) or (4), 25(1) or (2) or 26(1), (2), (3) or (8) shall be guilty of an offence and shall be liable on conviction to a fine not exceeding $20,000 or to imprisonment for a term not exceeding 12 months or to both.

PART 5

REVOCATION, AND SAVINGS AND TRANSITIONAL PROVISIONS

Revocation, and savings and transitional provision

30. Where a certificate has been issued under the Medicines (Clinical Trials) Regulations (Cap. 176, Rg 3) in relation to a clinical trial (other than one involving only medicinal products) and the certificate remains in force on [date of commencement of these Regulations], these Regulations apply, as from and including that date, to the trial to which the certificate relates —

(*a*) as if the trial is one for which the Authority has given authorisation under regulation 8;

(*b*) as if the sponsor of the trial is the sole sponsor of the trial for the purposes of these Regulations; and

(*c*) as if the date of expiry of the certificate is the date of the conclusion of the trial for the purpose of regulation 12.

THE SCHEDULE

Regulation 2(1)

PRINCIPLES OF GOOD CLINICAL PRACTICE

1. Clinical trials must be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with good clinical practice and the requirements of these Regulations.

2. Before a clinical trial is initiated, foreseeable risks and inconveniences must be weighed against the anticipated benefit for the subject and society, and a trial must be initiated and continued only if the anticipated benefits justify the risks.

3. The rights, safety, and wellbeing of the subjects of a clinical trial are the most important considerations and must prevail over interests of science and society.

4. The available non-clinical and clinical information on an investigational therapeutic product must be adequate to support the proposed clinical trial.

5. A clinical trial must be scientifically sound, and described in a clear, detailed protocol.

6. A clinical trial must be conducted in compliance with a protocol that has been approved by the relevant institutional review board.

7. The medical and dental care given to, and medical and dental decisions made on behalf of, subjects must always be the responsibility of a qualified practitioner with the relevant training and experience.

8. Each individual involved in conducting a clinical trial must be qualified by education, training, and experience to perform the individual's respective task.

9. Subject to these Regulations, freely given informed consent must be obtained from every subject prior to clinical trial participation.

10. All clinical trial information must be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.

11. The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with any applicable written law or rule or principle of law.

12. Investigational therapeutic products must be —

(*a*) manufactured, handled and stored, in accordance with such good manufacturing practice as may be specified by the Authority; and

(*b*) used in accordance with the approved protocol.

13. Systems with procedures that assure the quality of every aspect of the trial must be implemented.