MINISTRY OF HEALTH
SINGAPORE

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See 'Distribution List'

GUIDANCE ON CHARGING OF RESEARCH SUBJECT

This circular informs all institutions conducting Human Biomedical Research (HBR) under the Human Biomedical Research Act and their appointed Institutional Review Boards (IRBs) on the proposed guidance on the charging of research subjects.

2. MOH maintains that research subjects should **not** bear any costs for their participation in HBR. This is because HBR generally involves modalities that have insufficient clinical effectiveness or safety data over conventional comparative treatment.

3. However, we acknowledge that there may be challenges on the ground in distinguishing (i) the cost incurred from participation in research (i.e., "research costs") vis-à-vis (ii) the cost incurred by the research subject for management of their existing medical conditions, regardless of their participation in research (i.e., "routine costs"). There is also a lack of clarity on whether subjects who participate in research may be charged for treatment costs arising from adverse events (AEs), particularly if the subject has an underlying medical condition which the research was proposing to find a cure.

4. Research subjects participating in research could incur costs that may be categorised broadly as "research costs" and "routine costs" as defined below. Please refer to **Annex A** for further guidance on what would be considered **"research costs"** and **"routine costs"**.

a. **Research costs**" are defined as cost associated with "*procedures or services*[1] *that are being conducted for research that the subject would otherwise not have undergone or incurred if not for his or her participation in the study*". These may include (i) procedures and services conducted beyond what is normally required as part of routine care; and (ii) treatment costs of AEs related to the administration of the procedures and services as part of the research.

[1] These could include drugs, medical devices or laboratory or radiological tests.

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b. "**Routine costs**" are defined as cost associated with "*procedures or services that are part of routine care and would be conducted or incurred whether or not the research subject participates in the research*". This may include treatment costs related to the investigations or administration of medications relating to the existing medical condition of the patient, of which the patient will have paid for it, regardless of the patient's participation in the research.

CHARGING OF RESEARCH SUBJECTS

5. As research costs are only incurred due to participation in HBR, these should not be borne by the research subjects. This differs from routine costs that are incurred by patients regardless of their participation and should then be borne by the research subjects. In such circumstances, the following guiding principles apply:

a. **For research subjects who are recruited for research purposes and have no ongoing clinical care:** These are research subjects who are not receiving any clinical care related to the research. Hence, all costs associated with the subjects' involvement in the research should be considered research costs and borne by the researcher or sponsor. Research subjects should not be made to pay for any part of the cost.

b. **For research subjects who are recruited for research and have ongoing clinical care**: These are patients who are receiving clinical care related to the research and are recruited as research subjects to receive the "add on" intervention. Only procedures or services which are strictly not related to the research are considered routine care (i.e., "routine costs") and may be charged to the patient. The costs of any "add-on" research activities are considered research costs and should not be charged to the research subject.

CHARGING FOR TREATMENT COSTS ARISING FROM ADVERSE EVENTS

6. "**Adverse events**" are defined as untoward medical occurrences that occur to a research subject as a result of his or her participation in research. For AEs that arise during the conduct of HBR, treatment costs would by default be borne by the researcher or sponsor of the research study or covered by insurance as agreed between the researcher or sponsor and insurer, as the AE would likely not have occurred if the subject had not participated in the research. This applies in situations where an individual suffering from a serious or life-threatening disease participates in a research study with defined risks of AEs due to his or her underlying medical condition. This is regardless of the benefit-risk ratio associated with participation in the research being in favour of the alternative treatment.

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7. In the event of AEs, compensation[2] is to be covered by the researcher or sponsor. Compensation refers to payments made to research subjects for the treatment costs arising from AEs. Any terms and conditions related to the compensation, including the period covered by the researcher or sponsor after the study, should be reviewed and approved by an Institutional Review Board (IRB) that has been appointed by the research institution. IRB's assessment should take into account the ethical considerations based on the context of each research study and ensure that research subject's safety and welfare are prioritised.

INFORMATION TO BE PROVIDED TO RESEARCH SUBJECTS

8. Information on any anticipated research costs, routine costs, as well as compensation for any AEs must be provided and explained to the research subject or the person authorised to give consent on the research subject's behalf, before their participation in research. This explanation must occur prior to obtaining appropriate consent from the research subject or their authorised deputy. For clarity, such details should also be communicated and included in the Patient Information Sheet of the HBR study.

9. For further clarification on the above matter, please write in to hbr_enquiries@moh.gov.sg.

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[2] For clinical trials (CTs) regulated under the Health Products Act and Medicines Act, researchers may continue to refer to the Association of British Pharmaceutical Industry Clinical Trial Compensation Guidelines regarding AE compensation. Only in rare exceptions, where there is IRB's approval and research subjects have been informed and consented, may compensation for AEs borne by researcher or sponsor be waived, and research subjects be charged for treatment costs.

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Distribution List

(A) Research institutions (RIs) under the HBRA

1. A*STAR Research Entities	30. National Healthcare Group Pte Ltd
2. Advanced Medicine Imaging Private Limited	31. National Kidney Foundation
3. Agency for Integrated Care Pte Ltd	32. National University Health System
4. Amili Pte Ltd	33. National University of Singapore
5. Ang Mo Kio Thye Hua Kwan Hospital	34. National Youth Sports Institute
6. Chugai Pharmabody Research Pte Ltd	35. Ngee Ann Polytechnic
7. Cutis	36. Radlink Diagnostic Imaging (S) Pte Ltd
8. DotBio	37. Raffles Hospital
9. Dover Park Hospice	38. Renci Hospital
10. DSO National Laboratories	39. Republic Polytechnic
11. Eagle Eye Centre Pte Ltd	40. Research by Curie Oncology Ltd
12. Essilor R&D Centre Singapore	41. Singapore Armed Forces Medical Corps
13. Eye & Retina Surgeons	42. Singapore Chung Hwa Medical Institution
14. Gene Solutions Genomics Pte Ltd	43. Singapore Health Services Pte Ltd
15. HCA Hospice Limited	44. Singapore Institute of Technology
16. Health Promotion Board	45. Singapore Polytechnic
17. Health Sciences Authority	46. Singapore University of Social Sciences
18. Hummingbird Bioscience	47. Singapore University of Technology & Design
19. I & Vision Research Centre Pte Ltd	48. Sivantos Pte Ltd
20. Icon Cancer Centre	49. Sport Singapore
21. KYAN Therapeutics	50. St Andrew's Mission Hospital
22. Lilly Centre for Clinical Pharmacology Pte Ltd	51. ST Engineering Innosparks Pte Ltd
23. Lions Befrienders Service Association (Singapore)	52. St Luke's Hospital
24. Lucence	53. Stroke Support Station
25. Lundbeck Singapore Pte Ltd	54. Temasek Polytechnic
26. MiRXES Lab Pte Ltd	
27. Myopia Specialist Centre	
28. Nanyang Polytechnic	
29. Nanyang Technological University	

(B) Institutional Review Boards (IRBs) of RIs in (A)

1. Centralised Institutional Review Board, SingHealth
2. Domain Specific Review Board, NHG
3. DSO-SAF Institutional Review Board
4. Institutional Review Board, Advanced Medicine Imaging
5. Institutional Review Board, Agency of Integrated Care
6. Institutional Review Board, Agency for Science Technology & Research

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7. Institutional Review Board, AMILI
8. Institutional Review Board, Chugai Pharmabody Research
9. Institutional Review Board, National University of Singapore
10. Institutional Review Board, Nanyang Technological University
11. Institutional Review Board, Ngee Ann Polytechnic
12. Institutional Review Board, Nanyang Polytechnic
13. Institutional Review Board, Raffles Hospital
14. Institutional Review Board, Republic Polytechnic
15. Institutional Review Board, Singapore Institute of Technology
16. Institutional Review Board, Singapore Polytechnic
17. Institutional Review Board, Singapore University of Technology & Design
18. Institutional Review Board, Singapore University of Social Sciences
19. Institutional Review Board, Singapore Sports Institute
20. Institutional Review Board, St Luke's Hospital
21. Institutional Review Board, Temasek Polytechnic
22. Parkway Independent Ethics Committee, Parkway

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Annex A

GUIDANCE RELATING TO THE POLICY ON CHARGING OF RESEARCH SUBJECTS

(1) DISTINGUISHING BETWEEN RESEARCH COSTS AND ROUTINE CARE COSTS

1.1 Broadly, **research costs** are defined as "*costs incurred from procedures or services that are being conducted for research that the subject would otherwise not have undergone if not for his or her participation in the study*". Examples could include costs for the following:

a. Administration of the investigational new drug or devices (including placebos or comparators);
b. Items and services or procedures that are provided solely to satisfy data collection and analysis needs and that are not used in the direct clinical management of the research subject;
c. A service or procedure that is clearly inconsistent with widely accepted and established standards of care for a particular diagnosis;
d. Laboratory or radiological tests performed purely for research purposes e.g. imaging tests to assess liver damage as a result of the administration of the study drug (which is not usually performed for disease management); or
e. Hospital stays arising from participation in research.

1.2 Conversely, **routine care costs** are defined as "*costs incurred from procedures or services which are routine care and would be conducted whether or not the research subject participates in the research*". Examples could include costs for the following:

a. Visits to the subject's regular specialist for consultations for his or her condition;
b. Standard treatment for subject's existing disease or condition;
c. Hospital stays arising from subject's existing disease or condition;
d. Treatment to improve symptoms of the existing disease, or side effects of clinical treatment; or
e. Laboratory or radiological tests conducted for treatment of the subject's existing disease or condition.

(2) CASE STUDIES FOR REFERENCE

2.1 Please refer to the case scenarios below which aim to illustrate the abovementioned charging principles and help distinguish between research costs and routine care costs:

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Case Study 1 on distinguishing "research costs" vs "routine costs" for a subject who is recruited in a research study that is related to his or her medical condition: Enrolment of a subject with thyroid cancer in a Class 1 Cell Tissue and Gene Therapy (CTGTP) trial.

1. A subject with thyroid cancer who has completed treatment for his cancer is enrolled in a Class 1 CTGTP trial, which tests whether the CTGTP will aid in cancer remission.

2. In the scenario above, the following would be considered "**routine care costs**" and may be billed to the subject:
    a. Cancer treatment conducted as part of routine care.
    b. Specialist outpatient consultation fees for follow-up visits or consultations on the subject's thyroid cancer which is an existing condition.

3. Conversely, the following would be considered "**research costs**" and should be borne by the sponsor or researcher:
    a. Costs of administering the Class 1 CTGTP to the subject.
    b. Any additional tests on top of the routine care tests that the subject would not have undergone if not for participation in the research, e.g. immunotolerance test. This includes routine care tests that are conducted at higher frequencies than required for clinical treatment.

Case study 2 on distinguishing "research costs" vs "routine costs" for a subject that is recruited solely for research purposes: Enrolment of a subject with high blood pressure in a clinical research study of a medical device.

1. A subject with high blood pressure is recruited in a medical device research, which aims to test the safety and efficacy of a stroke rehabilitation medical device. The subject is asked to undergo DEXA scans and MRI scans of the spinal area and the scan results will be used for research purposes.

2. In the scenario above, costs of **all tests conducted in the research** (i.e. DEXA, MRI scans and any additional tests) would be considered "**research costs**" and should be borne by the sponsor or researcher. None of the costs would be considered "**routine costs**".

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