THE HMSC PREDICAMENT

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Last few months have been full of anticipation for the entities engaged in clinical trials in India. First, the Medical Council of India amended the ethical guidelines, banning hospitality to doctors, and while the industry players were still trying to figure out the dos' and donts' on this new turf, the Indian Council of Medical Research ("**ICMR**") started insisting upon approval of the Health Ministry's Screening Committee ("**HMSC**") and the known hospitals followed the suit.

A. SANCTITY OF HMSC:

HMSC does not appear to have an explicit legislative origin, and consequently a cloud of uncertainty looms over its sanctity, roles and responsibilities. HMSC and the requirements for its approval of clinical trials emerge from a combined effect of the following legislative and other documents:

I. The Drugs and Cosmetics Act, 1940 and Rules ("DCAR"):

The DCAR remains the primary legislation governing conduct of clinical trials in India. While the Act does not stipulate a prior approval of the HMSC, it does require abidance to the Ethical Guidelines for Biomedical Research on Human Participants (**"Ethical Guidelines"**), prescribed by the ICMR, in conduct of clinical trials.

II. Ethical Guidelines by ICMR:

The Ethical Guidelines refer to HMSC in chapters governing Ethical Review Procedure and Research in Transplantation. Given the scope and wordings (reproduced below), individual interpretations on the want of HMSC approval, are likely:

"Submission of Application

The researcher should submit an application in a prescribed format along with the study protocol as prescribed in SOP of IEC concerned. The protocol should include the following:-

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19. For international collaborative study details about foreign collaborators and documents for review of Health Ministry's Screening Committee (HMSC) or appropriate Committees under other agencies/ authority like Drug Controller General of India (DCGI)"

The above clause does not prescribe for specific approval of the HMSC, and uses the word "or", which could imply that the HMSC approval is an alternative to approvals of authorities like DCGI. Further, the scope of this clause is to list out the information to be provided to the Ethics Committee (**"EC"**), and not to prescribe for the approvals.

"Restricted Areas of Research

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2. Clinical trials sponsored by multinationals, involving stem cell products imported from abroad. Such collaboration shall require prior approval of the NAC-SCRT through IC-SCRT, IEC, DCGI and respective funding agency as per its procedure/Health Ministry's Screening Committee (HMSC)"

The above clause is within the chapter governing Research in Transplantation, and by its very language, governs only those trials where stem cell products are imported from abroad.

"International Collaboration

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5. *Collaboration will be permitted as per existing procedures of funding agencies (DBT, ICMR etc) or the Health Ministry's screening committee, even if no funding is involved after the joint proposal with appropriate MOU is approved by NAC-SCRT."*

While the above clause is also within the chapter governing Research in Transplantation, it even necessitates approval of the MOU by National Apex Committee for Stem Cell Research and Therapy (NAC-SCRT), which further restricts its application to specific trials only.

In view of the Ethical Guidelines, it may be argued that the approval of the HMSC may not be required for trials where the DCGI approval is obtained and the trial does not involve research in transplantation.

III. ICMR Documents:

The website of ICMR contains other documents, noteworthy among them being, the "Guidance for International Collaboration for Research in Biomedical Sciences" (the **"IC Guidelines"**) and "An Overview of International Collaborative Projects in Biomedical Research" (the **"Overview"**) that discuss the HMSC approvals.

The IC Guidelines discuss that an Indo-Foreign Cell (IFC) was set up by ICMR in the early 1980s to coordinate collaboration in biomedical research between India and other countries/ international agencies. The IFC was upgraded to the Division of International Health (IHD) in 2000. The scope of IHD appears to govern biomedical research/health sciences by way of bilateral agreements in the field of Science and Technology and specific agreements signed by the Ministry of Health and Family Welfare (**"MOHFW"**) with other countries as well as those signed directly by the ICMR. These agreements seek to govern (i) exchange of scientific information; (ii) exchange of scientists/technicians and joint execution of scientific projects, including support in the procurement of scientific equipments; and (iii) organisation of joint scientific meetings, seminars, workshops, symposia, on identified subjects of cooperation.

The IC Guidelines consequently provide that applications for research projects involving foreign assistance/ collaboration in biomedical/health research are to be submitted to ICMR(IHD) for approval of Government of India through HMSC.

The Overview also stipulates that "International collaborations are sought under bilateral, multilateral or regional framework modes for facilitating and strengthening interactions among governments, academia, institutions and industries in the areas of mutual interest."

The wording of the ICMR documents supports the general industry understanding that HMSC approval is applicable to collaboration projects between countries, or between Indian and foreign institutions pursuant thereto. Further, most of the bilateral documents referred to are with the foreign Government or medical institutes.

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It is however, noteworthy that the Overview provides a list of international collaborative projects approved by HMSC through the years 2000 to 2007, and the approvals obtained for studies by sponsors other than the medical institutes, Governments, charitable foundations and WHO, are negligible.

If HMSC approval was always required, an obvious question for the regulators would be the consequences of not following or enforcing the requirement for years altogether.

The term **"International Collaboration"** is however not defined by the Ethics Guidelines.

IV. The Government's Stance and ICMR Clarifications:

The Government however appears to be of neo-acquired view that HMSC approval is a must for all trials in India. A reflection of the Government's mindset is in its replies to certain queries posed for reply by the ICMR by a recent RTI application. Certain replies, in essence, are reproduced below:

"International trial/project" implies research being carried out with financial assistance from an "international funding agency", and/or there is technical collaboration between international partners. This could be bilateral or multilateral depending on the need and jurisdiction funding.

"International collaborative research/collaborative biomedical research" essentially refers to the meaning as

explained above. There is no enabling law to our knowledge that refers to these terms.

The "Guidance for International Collaboration for Research in Biomedical Sciences" gives an insight into the general information to be incorporated by Indian investigators while submitting proposals for international collaboration/ assistance; the requisite number of documents to be submitted; the necessary downloadable formats etc. The information is to assist the India biomedical scientists/researchers who intend to undertake international collaborative research. It is irrespective of their affiliation to private hospitals, NGOs or being investigators/sponsors from Indian subsidiaries of foreign pharmaceutical companies.

Though not expressly, but the above clarifications indicate towards the requirement for the Indian subsidiaries of foreign pharmaceutical companies to obtain HMSC approval. The ICMR has however admitted that there have not been any recent revisions to the prevalent guidelines.

V. Insistence by the Institutes:

The leading medical institutes in India involved in organising clinical trials, viz. the AIIMS, New Delhi, PGIMER, Chandigarh, etc. have reportedly taken a stern stand that HMSC approval is required in all cases of projects funded by private agencies. The AIIMS has in fact prescribed "Standard Operating Procedure for Projects Funded by Private Agencies at AIIMS" (**"SOP"**) in this regard.

The SOP does not distinguish between trial sponsorships by foreign and Indian entities, thus, extending the requirement of HMSC approval even to cases where the funding for trials stems from Indian subsidiaries of foreign companies.

With the biggies taking a firm stance, the rest of the hospitals are likely to follow their tracks. In the absence of any changes to the rules of the game, the reasons for sudden insistence by the Government however remain uncertain.

B. COLLATERAL ISSUES:

While the issue of HMSC approval continues to snowball given the want for legislative provisions and administrative clarity, a number of ancillary issues are emerging at the horizon.

Prime amongst them is the restriction being imposed by the ICMR on export of samples collected during the trials along with the requirement that the technology for the tests be transferred to Indian laboratories.

While the IC Guidelines introduce the aspect of exchange of human biological material for biomedical research, and the 'Guidelines for Exchange of Human Biological Material for Biomedical Research Purposes' (**"Material Exchange Guidelines"**) have been notified by the MOHFW in November 1997, the export restriction being imposed does not find specific mention in the related public documents. Somewhat to the contrary, the Material Exchange Guidelines state that the availability of facilities in India for carrying out certain investigations need not prevent collaboration with scientists in other countries for the same investigations, including with respect to transfer of samples.

The requirement for transfer of foreign technology to India also does not appear to be "well thought through", as it does not stipulate the situation where the sponsor may not own the testing technology.

The logic for the restrictive approvals granted by the HMSC may be assumed from the basic ideology followed by the MOHFW, that the intent of the trials should be to benefit the Indian population and the tests should be conducted in India, utilising or transferring the technology to India. However, legislative force behind the ideology is a requisite.

C. EVALUATION:

Given the current framework of regulation, one may argue that HMSC approval may not be strictly or mandatory required for general clinical trials in India by private entities.

However, the ICMR has adopted a strict view of late, that all studies wherein the entity that ultimately bears the expenses and will ultimately be the beneficiary of the study, is a foreign entity, prior approval of the HMSC will be required. Although there have been instances wherein many such studies have been conducted without obtaining prior approval of the HMSC, the requirement cannot now be voluntarily brushed aside and undermined unless an administrative clarification, whether or not triggered by a judicial supervision, is issued.

Else, one can hope that the proposed Biomedical Research on Human Participants (Promotion and Regulation) Bill, being codified by the ICMR, would accord some clarity on the issue.

Meanwhile, foreign sponsors or their Indian affiliates are being advised to seek approval of the HMSC for conducting the trials in India.